EXPLORING PEDIATRIC IMMUNIZATION MARKETS USING OPERATIONS RESEARCH AND GAME THEORY

BY

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DISSERTATION

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ABSTRACT

Vaccination is one of the most important and successful public health endeavors in human history, profoundly reducing mortalities caused by infectious diseases. In the United States, the comprehensive success of large scale pediatric immunization programs results from the collaboration of an interdependent system of government and industry stakeholders. A stakeholder in this system acts independently in pursuit of its own interests; yet, the actions of one stakeholder may profoundly affect the welfare of another stakeholder. It is imperative that these stakeholders understand the nature of their interdependence and the holistic impact of their behavior on the entire vaccine market. The market for pediatric vaccines is fragile and requires ongoing vigilance to meet public health goals regarding immunization coverage rates. Of particular concern is the economic competition within the vaccine industry, the impact of government regulatory policies on the vaccine industry, and the attendant impact on the vaccine system's ability to ensure the adequate provision of vaccines. This dissertation applies operations research and game theoretic methods to aid public health policy practitioners in making more informed decisions regarding the purchasing and pricing of vaccines in the public sector of the United States pediatric vaccine market. The market is analyzed from three different perspectives. First, an operations research approach is proposed for analyzing a pharmaceutical firm's pricing strategy for a single combination vaccine. A vaccine price is sought that maximizes a firm's expected revenue. Next, a game theoretic approach enables formulation of a static Bertrand pricing model that characterizes oligopolistic interaction between all of the firms in a multiple homogeneous product market. Sufficient conditions for the existence of a price equilibrium are provided. Finally, a monopsonistic buyer's vaccine formulary pricing and purchasing problem is formulated. Using a mixed integer non-linear program (MINLP) model, a pricing and purchasing policy for government health care policy practitioners can be designed that establishes a sustainable and stable capital investment environment in which the reliable provision of the pediatric vaccines so essential to public health can occur.

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For my wife and daughters.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Vaccination is one of the most important and successful public health endeavors in human history, profoundly reducing mortalities caused by infectious diseases [46, 49]. In the United States, the incidence of many childhood diseases has dramatically decreased, even as the number of diseases preventable by vaccination has increased [46]. The comprehensive success of large scale pediatric immunization programs results from the collaboration of an interdependent system of government and industry stakeholders. A stakeholder in this system acts independently in pursuit of its own interests; yet, the actions of one stakeholder may profoundly affect the welfare of another stakeholder. It is imperative that these stakeholders understand the nature of their interdependence and the holistic impact of their behavior on the entire vaccine market. The market for pediatric vaccines is fragile and requires ongoing vigilance to meet public health goals regarding immunization coverage rates [46]. Of particular concern is the economic competition within the vaccine industry, the impact of government regulatory policies on the vaccine industry, and the attendant impact on the vaccine system's ability to ensure the adequate provision of pediatric vaccines.

There are numerous stakeholders involved in the United States pediatric vaccine market. Pharmaceutical firms manufacture the vaccines. The Food and Drug Administration (FDA) licenses the use of the vaccines. The Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), and American Academy of Pediatrics (AAP) recommend proper use of the vaccines. The customers (i.e., healthcare providers, state and local government public health officials) purchase vaccines for the immunization of the patients (i.e., the consumers) under their care. Federal government public health officials negotiate the vaccine prices for the purchases made by the state and local governments. Pediatric vaccines purchased at the public sector price, as negotiated by the federal government, account for approximately 57% of total pediatric vaccine purchases by volume [46]. For the results presented in this dissertation, only the public sector of the market is considered. However, the methods discussed could also be applied to

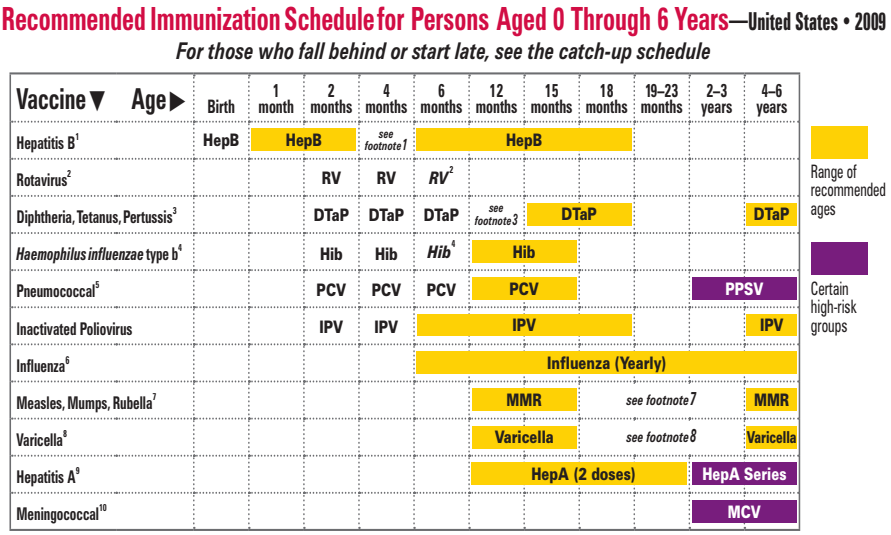
the private sector.

The pediatric vaccine industry consists of a relatively small number of pharmaceutical firms (i.e., companies, manufacturers) engaged in the research, development, manufacture, and distribution of pediatric vaccines. Participation in the vaccine industry is a difficult, costly, risky, and (most importantly), voluntary enterprise. All pediatric vaccines distributed in the United States are manufactured by privately held companies, with no obligation to sustain or initiate the production of pediatric vaccines, regardless of the importance of such vaccines to public health [18]. In the past forty years, the manufacture of pediatric vaccines has become less profitable due to rising costs and limited demand, inducing many pharmaceutical firms to exit the market [18, 45]. As of 2009, only four pharmaceutical firms manufacture vaccines for young children. Moreover, pediatric vaccines against seven diseases are manufactured by a single firm [20]. The contraction of the pediatric vaccine market negatively impacts the provision of the vaccines. When a vaccine is produced by a small number of manufacturers, production problems create immediate, acute shortages. In order to ensure adequate immunization coverage levels, a robust vaccine industry is paramount.

The FDA's licensing and approval process is a requirement for vaccine use in the United States. Following FDA approval, a positive recommendation is very important to the success of a pediatric vaccine. Changes in recommendations or requirements from the CDC, ACIP, or AAP greatly influence the demand for a particular vaccine. These organizations issue numerous guidelines regarding policies to effectively control vaccine-preventable diseases. This includes the CDC maintaining a list of acceptable vaccines and publishing an annual schedule concerning the appropriate periodicity and dosages of vaccines, the United States Recommended Childhood Immunization Schedule (RCIS) (see Figure 1.1 from CDC [12]).

Over the past two decades, the RCIS has grown increasingly complex, requiring children to endure numerous vaccine injections over the first two years of life. To fully meet the current RCIS may require up to twenty-four separate injections (not including Rotavirus, Influenza, Hepatitis A, and Meningococcal). Indeed, during a single clinical visit, at the two and six month well-child visit, a child may be required to receive up to five separate injections. Nonetheless, healthcare providers seek to satisfy the RCIS in order to ensure proper coverage for a given child and ultimately to provide public health protection for society at large. An important assumption held throughout this work is the premise that vaccine purchasers are rational and that over time, they will select vaccine formularies that satisfy the RCIS at the lowest overall cost, given their particular financial,

Figure 1.1: United States 2009 Recommended Childhood Immunization Schedule (through Age 6)



social, and immunization environment. It follows that the vaccine manufacturers desire to have their vaccines selected (and purchased) as a part of the lowest overall cost formulary, at the highest possible price.

Vaccine pricing remains a matter of conflict with respect to short-term consumer fairness and long-term industry efficiency. From the perspective of the pharmaceutical firms, high vaccine prices are warranted. Many experts [18, 38, 45, 46] suggest that manufacturers should earn adequate returns on their investments in order to sustain and expand the production of vaccines. From the perspective of the vaccine purchasers, low prices are needed. Experts contend [33, 38] that high prices may cause large groups of patients in publicly funded programs to go unvaccinated, leading to even higher costs to treat the subsequent expected increase in disease incidence rates.

This dissertation focuses on new approaches for aiding public health policy practitioners in examining the United States pediatric vaccine market. The pricing strategies of pharmaceutical firms in the public sector are explored. The pricing and purchasing policies of the monopsonistic federal government are also examined. The analysis presented enables government public health officials to make more informed decisions regarding regulatory policies concerning the pricing of pediatric vaccines. The appropriate pricing of pediatric vaccines is critically important to the success of public immunization programs. Lower prices facilitate higher immunization coverage rates while higher prices facilitate revenue streams that sustain the pharmaceutical industry's participation in the vaccine market. The dissertation is organized as follows.

Chapter 2 presents a literature review of earlier research where operations research techniques have been applied to the examination of the United States pediatric vaccine market. Other relevant topics related to the research are also discussed.

Chapter 3 examines pricing strategies for pediatric combination vaccines and their impact on the United States pediatric vaccine market. The methodology enables the analysis of pricing strategies of directly competing, partially overlapping, and mutually exclusive combination vaccines in the United States pediatric vaccine market, with the goal of maximizing each pharmaceutical company's expected revenue. The resulting analysis determines if a combination vaccine is competitively priced when compared to its competitors, for a given suite of federal contract prices. The proposed pricing approach suggests an appropriate price for a given combination vaccine, whereby a substantial increase in expected revenue can be realized.

Chapter 4 presents a static Bertrand oligopoly pricing model that characterizes oligopolistic interaction between asymmetric firms in a multiple homogeneous product market with a novel demand structure. The treatment of the novel nature of the demand structure is the matter of interest where firms satisfy demand by selling bundles of one or more products and consumers seek to purchase at least one of each product at an overall minimum cost. Demand is captured by defining a weighted set covering problem (WSC) instance, with the weights (prices) dynamically controlled by firms engaged in Bertrand competition. A Nash equilibrium is sought in order to analyze the depicted market. Complicating the analysis is the overlapping and interdependent nature of the bundles of products and the discontinuity of the payoff in the price of each bundle. An iterative improvement algorithm is defined that enables construction of pure strategy Nash equilibrium price-tuples. Sufficient conditions for the existence of pure strategy Nash equilibria (some in the limiting sense) are provided, indicating that this class of game always yields at least one pure strategy equilibrium. The temporal assumption of the model is relaxed to allow for repeated interaction between the competing firms. The repeated game version of the model enables examination of tacit collusion in an underlying market of interest. The utility of the models is demonstrated by analyzing the public sector of the United States pediatric vaccine market.

Chapter 5 presents an operations research approach that addresses the issue of the pediatric vaccine industry's continuing viability from the perspective of the CDC. The monopsonistic market power of the federal government uniquely positions it to significantly influence the pediatric vaccine market by negotiating contractual agreements that increase the vaccine manufacturers' financial

incentives to remain in the market. The Altruistic Monopsonist Vaccine Formulary Pricing and Purchasing Problem (AMVF3P) is introduced, which seeks pediatric vaccine prices and purchase quantities that ensure a birth cohort is fully immunized according to the recommended childhood immunization schedule at an overall minimum system cost while also ensuring that vaccine manufacturers each attain a reasonable level of profit. The practical value of AMVF3P is demonstrated by analyzing and assessing different pricing and purchasing policies that the CDC could adopt in attempting to actively manage the long-term provision of pediatric vaccines.

Chapter 6 presents a brief conclusion and identifies areas for future research.

CHAPTER 2

LITERATURE REVIEW

This chapter provides a literature review of past research where operations research was used to examine pediatric immunization markets and is applicable to the research efforts presented in Chapters 3 and 5. Another relevant topic related to the research presented in this dissertation is also discussed, specifically, background information on game theory, which is applicable to the research effort presented in Chapter 4.

2.1 Operations Research and Pediatric Immunization Markets

This section reviews the operations research literature as it applies to the examination of pediatric immunization markets. Operations research methods have been applied to the analysis of the United States pediatric vaccine market. Prior research has mostly addressed the selection of an optimal vaccine formulary (i.e., a set of vaccines) that satisfies a RCIS at minimum cost [27, 30, 61] (from the perspective of a vaccine purchaser) or the determination of optimal vaccine prices [29, 31, 51, 55, 56] (from the perspective of a vaccine manufacturer).

Weniger et al. [61] introduce an integer program (IP) model to aid health care decision makers in determining a vaccine formulary that minimizes the cost to fully immunize a child according to a given childhood immunization schedule. Jacobson et al. [30] present a full technical description of the model introduced by Weniger et al. [61]. Hall et al. [27] introduce the general vaccine formulary selection problem, providing fundamental insights into the structure of problems concerning minimum cost satisfaction of a childhood immunization schedule.

Sewell et al. [56] adopt a "reverse engineering" scheme involving a bisection algorithm to compute a vaccine's maximum inclusion price (i.e., the maximum price at which a vaccine is selected to be part of the lowest overall cost formulary). The algorithm can be adjusted to investigate pricing and purchasing questions; it enables determination of the lowest overall cost formulary, the set of vaccines that satisfies the RCIS at the overall minimum formulary cost. The algorithm accounts for

a number of different applicable cost components, one of which is the purchase price of individual vaccines. The other cost components are clinical visitation costs, vaccine preparations costs, and a vaccine administration cost also known as the cost of an injection. Sewell and Jacobson [55] present a full technical description of the methods in Sewell et al. [56]. Similar efforts are seen in Jacobson et al. [29, 31]. While these efforts provide analysis tools to help one group of stakeholders in the pediatric vaccine market make decisions, no study has presented a comprehensive approach in which the interests of all stakeholders in the market are simultaneously considered.

2.2 Game Theory

Noncooperative game theory provides an appropriate technique for analyzing economic conflict between firms when no collusion is allowed [59]. A firm's determination of the proper pricing strategy when its profits are affected by the pricing decisions of other firms in the market lends itself well to game theory. Myerson [41] defines game theory as the study of mathematical models of conflict and cooperation between intelligent and rational decision-makers (firms). An *intelligent* firm knows everything there is to know about the game. A *rational* firm acts in a consistent manner pursuant to its own objectives (i.e., it seeks to maximize its own profit). The motivating principle of this method of analysis is the understanding of the fundamental issues underlying the real market of interest.

Models of oligopolistic interaction depict a finite and typically small number of firms competing in a homogeneous product market. The strategic variable of interest for each firm depends on the specific model that is implemented. In the classical model put forth by Bertrand [3], each firm's strategic variable is the price of the homogeneous product. The market reacts to the offered prices by first demanding an attendant quantity and then clearing by some unspecified mechanism. It is assumed that the lowest price firm(s) must supply the entire market demand. In contrast, in the classical model proposed by Cournot [15], each firm's strategic variable is its quantity produced. The market reacts to the aggregate production level of the firms by first setting a price and then clearing by some unspecified mechanism. Note that market *clearing* refers to the process by which markets gravitate towards prices that balance quantity supplied and quantity demanded, such that in the long run, the market is *cleared* of all surpluses and shortages.

The appropriateness of a model depends on the basic structure of the market of interest. For example, the Bertrand model is well suited to production-to-order markets (e.g., various service

industries) [48]. Conversely, the Cournot model is well suited to production-to-stock markets (e.g., agricultural products, automobiles). Vives [59] also notes that the industry variable that is more difficult to adjust mid-process, due to contractual obligations or other extenuating circumstances, could be the dominant strategic variable, even in industries where the other strategic variable is typically dominant. Indeed, the motivating domain problem of interest in this dissertation reflects such a situation. In the United States pediatric vaccine market, pharmaceutical companies manufacture vaccines on a production-to-stock basis, yet the industry is best modeled as a Bertrand competition since vaccine prices (in the public sector) are fixed for one year periods due to contractual obligations negotiated by the Centers for Disease Control and Prevention (CDC).

A review of the relevant literature suggests a need for a model treating a market exhibiting a demand structure with a highly combinatorial and interdependent nature. The model presented in Chapter 4 allows for the analysis of markets in which consumers face a weighted set covering (WSC) optimization problem (in which a minimum cost set cover is sought) with several competing firms setting the applicable weights in the problem (in order to maximize individual firm profit). The WSC problem is: given S, a set of elements, and B, a set of weighted subsets of S, find a minimum cost collection C of subsets from B such that C covers all elements in S.

No game has been formulated in the literature to account for markets with such a demand system. While many studies concentrate on pricing behavior in markets with multiproduct firms, studies typically consider markets with differentiated products and demand systems portrayed by smooth (or at least, twice differentiable) functions [58, 59]. Distinguishing characteristics of the results presented in this dissertation involve the structure of the demand system; a smooth demand function is attributed only to the aggregate cost of the minimum weighted cover (i.e., the group of bundles of homogeneous products). An additional combinatorial complication results from the overlapping bundles of products offered by the competing firms. Demand for any given bundle is determined by the set of solutions to the defining WSC problem, indicating the discontinuous nature of the market structure.

A solution concept is a rule for specifying predictions concerning the expected behavior of players in a game [41]. In this research effort, the solution concept to the formulated game is the Nash equilibrium [43]. The classical Bertrand equilibrium is easily seen as a forerunner to the modern game theory solution concept provided by Nash. The goal of Chapter 4 is to examine the fundamental questions regarding the proposed game to include the existence of pure strategy Nash equilibria

and the computation of such equilibria. Note that mixed strategy equilibria are not desirable (and are not considered in this effort) due to their problematic economic interpretation. The nondeterministic selection of the support strategies and the corresponding lack of a clear incentive to use the prescribed mixed strategy in an equilibrium prevents decision-makers from fully supporting a mixed strategy policy. As Vives [59] notes, it is doubtful that firms select optimal strategies by rolling dice.

When examining markets using a Bertrand framework, it is important to consider three critical assumptions. The first assumption relates to production capacity; Bertrand competition assumes that any firm can fully satisfy market demand. The second assumption relates to the temporal aspect of the competition; firms supposedly engage in competition only once. The third assumption relates to product differentiation; the firms' products are assumed to be perfect substitutes for one another. Together, these assumptions depict an extreme economic situation in which only two firms are required to induce a perfectly competitive result (i.e., prices fall to marginal cost, providing very low economic profit to the competing firms). Moreover, due to the stringency of the assumptions, the resulting Nash equilibrium is often economically naive and unrealistic. To address these concerns, the temporal aspect of the model presented in Chapter 4 is relaxed to allow for repeated interaction between the firms. This relaxation provides a noncooperative game theoretic mechanism to expand the set of Nash equilibria to include more realistic behavior.

CHAPTER 3

PRICING STRATEGIES FOR COMBINATION PEDIATRIC VACCINES

Routine administration of pediatric vaccines is considered one of the most effective means of preventing infectious diseases. In the United States, the Centers for Disease Control and Prevention (CDC) acts as the primary public health organization responsible for setting pediatric immunization policy. The CDC has identified a number of compelling reasons for the use of combination vaccines in pediatric immunization [8]. This includes reducing the number of injections necessary to satisfy the United States Recommended Childhood Immunization Schedule (RCIS), reducing pain and discomfort experienced by children, and the potential to increase vaccination compliance rates [34, 35, 40, 39].

The CDC has issued numerous guidelines concerning the proper methods and scheduling for vaccinating a child. The Advisory Committee on Immunization Practice (ACIP), an advisory body to the CDC, provides specific guidance regarding policies to effectively control vaccine-preventable diseases. This includes maintaining a list of acceptable pediatric vaccines as well as publishing an annual schedule regarding the appropriate periodicity and dosages [9, 5].

Over the past two decades, the RCIS has grown increasingly complex, requiring children to endure numerous vaccine injections over the first two years of life. To fully meet the current RCIS (see Figure 1.1 from CDC [12]) may require up to twenty-four separate injections (not including Rotavirus, Influenza, Hepatitis A, and Meningococcal). Indeed, during a single clinical visit, at the two and six month well-child visit, a child may be required to receive up to five separate injections. Nonetheless, healthcare providers seek to satisfy the RCIS in order to ensure proper coverage for a given child and ultimately to provide public health protection for society at large.

In the United States pediatric vaccine market, four pharmaceutical companies manufacture all the vaccines required to successfully complete the RCIS. The analysis that follows concentrates only on diseases for which there are competing vaccines produced by different pharmaceutical companies (i.e., when two or more vaccines can satisfy the dosage requirement during a given time period,

they are said to compete). For the four competitive antigens, three pharmaceutical companies compete pairwise with each other over the sale of seven monovalent and five combination vaccines (Table 3.1).

Table 3.1: 2009 CDC licensed pediatric vaccines by pharmaceutical company (competitive antigens only)

Sanofi Pasteur	GlaxoSmithKline	Merck
DTaP	DTaP	HepB
Hib	HepB	Hib
IPV	DTaP-IPV	Hib-HepB
DTaP/Hib	DTaP-HepB-IPV	
DTaP-IPV/Hib		

Pharmaceutical companies have developed combination pediatric vaccines that immunize against multiple diseases in a single injection. Several combination pediatric vaccines have been licensed for use within the United States. For example, Comvax (Hib-HepB), manufactured by Merck (Comvax is a registered trademark of Merck), contains antigens providing protection against Haemophilus influenzae type B and hepatitis B, TriHIBit (DTaP/Hib), manufactured by Sanofi Pasteur (TriHIBit is a registered trademark of Sanofi Pasteur), contains antigens providing protection against four diseases: diphtheria, tetanus, pertussis, and Haemophilus influenzae type B, and Kinrix (DTaP-IPV), manufactured by GlaxoSmithKline (Kinrix is a registered trademark of GlaxoSmithKline), contains antigens providing protection against four diseases: diphtheria, tetanus, pertussis, and polio. The first pentavalent vaccine, Pediarix (DTaP-HepB-IPV), manufactured by GlaxoSmithKline (Pediarix is a registered trademark of GlaxoSmithKline), contains antigens providing protection against five diseases: diphtheria, tetanus, pertussis, hepatitis B, and polio. From December 2002 until the summer of 2008, Pediarix was the only pentavalent combination vaccine available in the market. However, that changed in June 2008, when the Food and Drug Administration (FDA) approved a second pentavalent combination vaccine, Pentacel (DTaP-IPV/Hib), manufactured by Sanofi Pasteur (Pentacel is a registered trademark of Sanofi Pasteur), which contains antigens providing protection against diphtheria, tetanus, pertussis, polio, and Haemophilus influenzae type B. The structure of the RCIS makes it unrealistic for both Pediarix and Pentacel to be used simultaneously in a single pediatric immunization formulary. It follows that the immunization market will gravitate to the combination vaccine providing the best economic value in terms of overall cost, which in turn leads to three important (and related) questions. From the perspective of the healthcare providers, what set of vaccines fully satisfies the RCIS at minimum cost? Should a vaccine formulary be formed around Pediarix or Pentacel? From the perspective of the pharmaceutical companies, what prices should be set for their vaccines in order to maximize revenue? Therefore,

the pricing strategies of Pediarix and Pentacel are of direct interest.

This chapter describes how the vaccine selection algorithm introduced by Jacobson et al. [30] can be used to investigate a pharmaceutical company's pricing strategy for a pediatric combination vaccine and gain insight into the subsequent attendant market conditions. The main contribution of the chapter is to provide a methodology for objectively evaluating two partially overlapping combination vaccines (e.g., DTaP-HepB-IPV and DTaP-IPV/Hib) based on price and (uncertain) cost of injection information. Furthermore, the analysis addresses how a pharmaceutical company should price such a vaccine in order to maximize its expected revenue per child (ERPC), which quantifies the amount of revenue the pharmaceutical company can expect to earn per child fully immunized according to the RCIS, and hence, is a proxy measure for the long term market prospects of a company's suite of vaccines.

The approach in this chapter focuses on maximizing revenue for products that have low marginal costs. The fundamental premise is that a pharmaceutical company's capital expenditures associated with the research, development, and start-up production of a new pediatric vaccine are treated as sunk costs. Having already made the decision to enter the market, competitive market forces now dictate appropriate pricing, not the price best suited to recover sunk cost. Actual marginal costs of production are assumed to be very low. Consequently, with low marginal costs it is reasonable to equate revenue with profit. Moreover, note that there is no demand elasticity. Demand is fixed, based on CDC recommendations concerning routine administration of licensed pediatric vaccines (a healthcare provider must satisfy the RCIS). For a fixed cost of injection, a pharmaceutical company's revenue can only be increased at the expense of another company's revenue. The premise here is that over time, healthcare providers will build their formularies around the combination vaccine resulting in the lowest overall cost, given their particular financial, social, and immunization environment. This perspective, as captured by each pharmaceutical company's expected revenue for each child completing his or her RCIS, is articulated as the pediatric vaccine market.

The methodology employed in this chapter builds upon the results reported in [55, 56] by analyzing the conditions in a Pediarix-only market and one in which both Pediarix and Pentacel are available for purchase. Naturally, this general approach is applicable to any partially overlapping combination vaccine (e.g., Comvax) for which there is competition. The target audience includes those within the pediatric healthcare community seeking information regarding the relative economic value, effective pricing strategies, and impact of combination vaccines on market conditions.

The chapter is organized as follows: Section 3.1 describes the methods used to analyze the conditions in a market without Pediarix and Pentacel (prior to December 2002), a Pediarix-only market (December 2002 to June 2008), and a market in which both Pediarix and Pentacel are available for purchase (June 2008 to present). A pricing strategy is then proposed for Pentacel, whereby its manufacturer, Sanofi Pasteur, seeks to maximize its ERPC. Section 3.2 reports the results of the analysis, including the economic value of Pediarix and Pentacel. Additionally, an approach is suggested for pricing Sanofi Pasteur's Pentacel in order to increase its ERPC. Section 3.3 provides concluding comments and directions for future research.

3.1 Methods

Jacobson et al. [30] propose an integer programming model to obtain the lowest overall cost formulary needed to satisfy a subset of the RCIS. The lowest overall cost formulary is the set of vaccines that satisfies the RCIS at minimum cost, where cost includes the purchase price of individual vaccines, clinical visitation costs, vaccine preparations costs, and a vaccine administration cost (the cost of an injection). The model has been enhanced and updated to consider all monovalent and combination vaccines that were licensed in the United States and under federal contract (ending 31 March 2010) for purchase by the CDC for use in United States public-sector immunization program (Table 3.2) [5, 19]. The analysis in this chapter uses only federal contract prices (typically lower than private sector prices), although the methods discussed could also be applied using private sector prices for the vaccines.

Table 3.2: List of existing competitive vaccines and attendant features

Vaccine		Packaging	Price per dose	Prep. cost per dose	Subtotal	Manufacturer
DTaP	Tripedia	[v]	$13.25	$ 0.75	$14.00	Sanofi Pasteur
DTaP	Infanrix	[s]	$13.75	$ 0.25	$14.00	GlaxoSmithKline
DTaP-IPV	Kinrix	[s]	$32.25	$ 0.25	$32.50	GlaxoSmithKline
DTaP-HepB-IPV	Pediarix	[s]	$48.75	$ 0.25	$49.00	GlaxoSmithKline
DTaP/Hib	TriHIBit	[v]	$27.31	$ 0.75	$28.06	Sanofi Pasteur
DTaP-IPV/Hib	Pentacel	[v]	$51.49	$ 0.75	$52.24	Sanofi Pasteur
IPV	IPOL	[s]	$11.51	$ 0.25	$11.76	Sanofi Pasteur
HepB	ENGERIX B	[s]	$9.75	$ 0.25	$10.00	GlaxoSmithKline
HepB	RECOMBIVAX	[v]	$10.00	$ 0.75	$10.75	Merck
Hib-HepB	COMVAX	[v]	$28.80	$ 0.75	$29.55	Merck
Hib	COMVAX	[v]	$28.80	$ 0.75	$29.55	Merck
Hib	ActHIB	[v]	$8.66	$ 0.75	$9.41	Sanofi Pasteur

Note that monopoly vaccine manufacturers and their products are not included in the analysis. The vaccine selection algorithm trivially selects the single product available and therefore no meaningful analysis is accomplished, as no competition occurs. Merck's measles, mumps, and rubella

(MMR) combination vaccine and Wyeth/Lederle's Pneumococcal Conjugate 7-valent (PCV7) vaccine are examples of monopoly products excluded from this analysis.

Four objective function components determine the overall cost for an immunization formulary that fully satisfies the RCIS: the purchase prices of the vaccines, the estimated cost of a clinic visit, an estimated cost for vaccine preparation time by nurses, and an estimated cost of administering an injection [55, 56]. The cost of a clinic visit remains the same as in previous studies [30, 61], though since all relevant time periods require a visit, this value does not impact the selection of the lowest overall cost formulary.

The cost of administering an injection is a highly subjective value [61]. Unlike previous studies [31, 55, 56] which treated it as a constant (albeit varied across a range of values), a probabilistic distribution is chosen here so as to better represent a user's beliefs regarding the intrinsic value associated with reducing the number of injections a child must endure in order to complete the RCIS. Due to the highly subjective nature of the cost of an injection, a well fit, empirically backed distribution is unavailable. The dearth of data suggests a more general selection is warranted. The analysis in this chapter uses a triangular distribution with a minimum of \$6, a mode of \$10, and a maximum of \$14, though any distribution may be considered.

Vaccine preparations costs for vials [v] and syringes [s] were \$0.75 and \$0.25 per dose, respectively (Table 3.2) (see [30, 61] for detailed descriptions and explanations). Qualitative factors affecting the vaccine selection process were not included in this study due to the difficulty in quantifying their values. Issues such as vaccine brand loyalty (where lowest overall cost alone does not dictate vaccine selection) and vaccine formulary inertia (where an incumbent formulary remains a health provider's choice despite the cost saving merits of a competing, lower cost formulary, due to resistance to change) can be adequately formulated but the associated parameters remain difficult to quantify. Only cost factors provide an objective measure of comparison between two competing combination vaccines and their attendant formularies.

The integer programming model introduced by Jacobson et al. [30] enforces the structure and rules of pediatric immunization (periodicity and dosage constraints) as recommended by the ACIP [9, 12]. The six time periods of interest include: birth-month, month 2, month 4, month 6, month 12-18, and year 4-6 periods. The four vaccine components of interest are DTaP, HepB, Hib, and IPV. A vaccine can only be administered for diseases and in time periods for which it has been licensed by the FDA [19]. Examples of ACIP recommendations include: manufacturer brand

matching for the month 2, 4, and 6 doses of DTaP, whereby each of the doses of DTaP for the pertinent three time periods must be of the same brand [8]. Administering Merck's Hib in the month 2 and 4 time periods implies that the month 6 dose is not required [12]. Extraimmunization with additional doses beyond those required is permissible in the model [30]. In each of the market scenarios investigated, it is assumed that a monovalent HepB vaccine birth dose is administered to all newborns prior to discharge from the hospital.

Three different market scenarios are analyzed. Scenario 1 examines a market in which Pediarix and Pentacel are both unavailable (i.e., prior to December 2002). The ERPC for each pharmaceutical company is reported. The results of Scenario 1 provide a base case for comparison with Scenario 2, which examines market conditions in which only Pediarix is available. Comparing the results provides insights into the economic value of Pediarix. Scenario 2 reflects market conditions as they stood prior to the entry of Pentacel (on 23 June 2008) into the market. Scenario 3 examines a market in which both Pediarix and Pentacel are available for purchase and reflects the current (i.e., for vaccines with federal contract prices ending 31 March 2010) market conditions. A pharmaceutical company's relative contribution to the total ERPC earned for competitive antigens provides insight into natural market tendencies in the long term. That is to say, one would expect pediatric vaccine purchasers to gravitate towards the formulary that provides them full immunization coverage for the lowest overall cost, given their belief concerning the distribution of cost of injection (C) for their patient population. The ERPC is expressed as:

$$E[RPC_{Mfg}(C)] = \int_{C_{Min}}^{C_{Max}} RPC_{Mfg}(c) f(c) dc, \tag{3.1}$$

where f is the density function for $C \sim \text{triangular}(C_{Min} = 6, C_{Mode} = 10, C_{Max} = 14)$ and $RPC_{Mfg}(c)$ is the revenue per child earned by vaccine manufacturer (pharmaceutical company) Mfg at a cost of injection c. The process of determining $RPC_{Mfg}(c)$ requires reverse engineering of the vaccine selection algorithm in order to find the lowest overall cost formulary across the range of values for C; this typically involves solving between 50 and 100 integer programs using CPLEX.

An approach for pricing a pediatric vaccine is presented to ensure that a pharmaceutical company achieves its highest possible ERPC given its belief concerning the distribution of the cost of an injection for its customers and the prices of vaccines manufactured by other pharmaceutical companies. A pharmaceutical company could very well adjust the price of all the vaccines it controls. The focus of this chapter is on combination vaccines however, so the approach is employed

changing only one vaccine price at a time; the maximizing expected revenue per child (MERPC) approach is demonstrated on Pentacel in Scenario 4, with both Pediarix and Pentacel available for purchase and reflects the current (i.e., for vaccines with federal contract prices ending 31 March 2010) market conditions. The MERPC approach can be expressed as

$$\arg\max_{p} \left(E[RPC_{SP}(p, C)]\right), \tag{3.2}$$

where,

$$E[RPC_{SP}(p, C)] = \int_{C_{Min}}^{C_{Max}} RPC_{SP}(p, c) f(c) dc, \tag{3.3}$$

and where p is the price of Pentacel, and $RPC_{SP}(p, c)$ is the revenue per child earned by Sanofi Pasteur when the cost of an injection equals c and Pentacel costs p dollars per dose. One could solve Equation (3.2) by exhaustive enumeration, though when multiple vaccine prices are adjusted simultaneously, such a solution method quickly becomes computationally infeasible. For this analysis, a bisection search algorithm was employed to reduce the number of integer program solutions needed to obtain the revenue per child values. The MERPC approach typically requires thousands of integer programs to be solved to identify a vaccine price that maximizes ERPC.

3.2 Results and Analysis

This section reports the results of reverse engineering the vaccine selection algorithm to gain insights into the United States pediatric vaccine market. Sections 3.2.1-3.2.3 report the results of Scenarios 1-3, respectively. Section 3.2.4 reports the results of Scenario 4, providing details concerning a proposed pricing strategy for Pentacel whereby Sanofi Pasteur prices Pentacel under current (i.e., for vaccines with federal contract prices ending 31 March 2010) market conditions so as to maximize its ERPC. The general approach applies to any pharmaceutical company for any of its pediatric vaccines. Comparing Sanofi Pasteur's ERPC after pricing Pentacel using the MERPC approach, with its performance reported in Scenario 3, reveals that the initial federal contract price for Pentacel should be lowered to increase Sanofi Pasteur's ERPC.

3.2.1 Market Conditions without Pediarix and Pentacel

Scenario 1 considers a pediatric vaccine market in which both Pediarix and Pentacel are unavailable. This scenario reflects actual conditions in the market prior to the licensing of Pediarix in December 2002. The vaccine selection algorithm solves for the lowest overall cost formulary for a fixed cost of an injection, across the specified range of values for the cost of an injection. The cost of an injection bounds for which a formulary remains lowest overall cost (referred to as the cost of injection interval) are determined using a bisection search algorithm. The bounds for the cost of an injection are constrained by the minimum and maximum values of its chosen distribution. For this analysis, the cost of an injection is distributed triangular, with a minimum of \$6, a mode of \$10, and a maximum of \$14. The vaccines and their associated costs are listed in Table 3.2.

Scenario 1 results (see Table 3.3) indicate the presence of two lowest overall cost formularies. The Monovalent+TriHIBit Formulary is the lowest overall cost formulary for $C \in [\$6.00, \$7.51]$. This formulary uses all monovalent vaccines to satisfy the RCIS, with the exception of Sanofi Pasteur's TriHIBit in the month 12-18 period. As discussed previously, the monovalent vaccines do well at lower costs of injection because the intrinsic premiums associated with the combination vaccines have not yet been overcome by the cost of an injection. For this formulary, TriHIBit, a combination vaccine itself, is priced (\$28.06 per dose, post-preparation) close to the sum of its component monovalent vaccines (\$23.41, post-preparation) and is thus economically attractive for a \$6.00 cost of an injection, the lowest value of interest for the cost of an injection in this analysis. Recall that Merck competes for two of the four contested antigens (HepB and Hib; see Table 3.1). In this formulary two injections of its Hib monovalent are selected, which eliminates the requirement for the Hib dosage in the month 6 period, creating an economic benefit over the competing Sanofi Pasteur Hib monovalent (i.e., although the Sanofi Pasteur Hib is less expensive, it requires three doses versus Merck's two, and hence, is not as cost effective). GlaxoSmithKline competes for three of the four contested antigens (though in this scenario, it competes only for DTaP and HepB, since Pediarix is unavailable). In this formulary, its monovalent HepB is selected, since it is simply less expensive than the competing Merck HepB monovalent. Its DTaP monovalent is credited with 2.5 of the five doses in the RCIS, since both it and Sanofi Pasteur's DTaP have a post-preparation cost per dose of \$14.00. Sanofi Pasteur competes for three of the four contested antigens and is the dominant manufacturer in this formulary. Its DTaP monovalent is tied with the competing GlaxoSmithKline DTaP monovalent and is selected for 2.5 of the five doses in the RCIS.

Table 3.3: Lowest overall cost formulary with associated pharmaceutical company revenue per child earned (Scenario 1)

Monovalent + TriHIBit® Formulary					COMVAX® Formulary			
Cost of injection interval			$ 6.00	$ 7.51	Cost of an Injection interval		$ 7.51	$ 14.00
Pharmaceutical Company	Time Period	Vaccine	Revenue		Vaccine	Notes	Revenue	
Merck	Birth	-			-			
	Month 2	Hib	$ 11.29		**Hib-HepB**	Hib exits	$ 28.80	
	Month 4	Hib	$ 11.29		Hib		$ 11.29	
	Month 6	-			-			
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	-		$ 22.58	-			$ 40.09
GlaxoSmithKline	Birth	HepB	$ 9.75		HepB		$ 9.75	
	Month 2	DTaP, HepB	$ 16.63		DTaP	HepB exits	$ 6.88	
	Month 4	DTaP	$ 6.88		DTaP		$ 6.88	
	Month 6	DTaP, HepB	$ 16.63		DTaP, HepB		$ 16.63	
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	DTaP	$ 6.88	$ 56.75	DTaP		$ 6.88	$ 47.00
Sanofi Pasteur	Birth	-			-			
	Month 2	DTaP, IPV	$ 18.14		DTaP, IPV		$ 18.14	
	Month 4	DTaP, IPV	$ 18.14		DTaP, IPV		$ 18.14	
	Month 6	DTaP, IPV	$ 18.14		DTaP, IPV		$ 18.14	
	Month 12-18	DTaP/Hib	$ 27.31		DTaP/Hib		$ 27.31	
	Month 19-36	-			-			
	Month 48-72	DTaP, IPV	$ 18.14	$ 99.85	DTaP, IPV		$ 18.14	$ 99.85

Since Pediarix is unavailable for this scenario, the Sanofi Pasteur IPV monovalent is a monopoly product and is trivially selected for all four doses. Sanofi Pasteur earns \$99.85 of revenue per child completing the RCIS using this formulary, compared to \$28.50 for GlaxoSmithKline and \$22.58 for Merck.

The COMVAX Dominant Formulary is the lowest overall cost formulary for $C \in [\$7.51, \$14.00]$. A cost of an injection of \$7.51 is sufficiently high enough that the inclusion of COMVAX becomes economically viable. Thus it enters the lowest overall cost formulary at a cost of an injection of \$7.51, displacing one injection of Merck's Hib and one injection of GlaxoSmithKline's HepB. This results in a transfer of revenue from GlaxoSmithKline to Merck due to the superiority of the combination vaccine COMVAX. Merck realizes the COMVAX premium while acquiring one of GlaxoSmithKline's monovalent HepB doses. The remainder of the formulary remains unchanged when compared to the Monovalent+TriHIBit Formulary. While Merck increases revenue at the expense of GlaxoSmithKline, Sanofi Pasteur remains the dominant manufacturer. Sanofi Pasteur still earns \$99.85 of revenue per child, completing the RCIS using this formulary, compared to \$47.00 for GlaxoSmithKline and \$40.09 for Merck.

In Scenario 1, the COMVAX Dominant Formulary has the largest impact on the ERPC for the three competing pharmaceutical companies. The COMVAX Dominant Formulary is the lowest overall cost formulary for $C \in [\$7.51, \$14.00]$. This means that approximately 93% of the customers

who value the cost of an injection as represented by a triangular(6,10,14) prefer the COMVAX Dominant Formulary to serve as their lowest overall cost formulary. The ERPC for the three competing pharmaceutical companies can be computed using Equation (3.1). Recall that the revenue of interest is only for the four antigens for which there is competition, with Sanofi Pasteur obtaining 53.6% of the ERPC, GlaxoSmithKline 25.6%, and Merck 20.8%. Sanofi Pasteur competes for three of the four antigens, totaling 13 doses, providing higher potential for earned revenue. Merck also does well, considering it is only competing for two of the four antigens totaling just seven doses. Note that GlaxoSmithKline, without Pediarix, earns \$47.69 of ERPC. This baseline expected revenue will be compared to its expected earnings in Scenario 2, where Pediarix is available.

3.2.2 Market Conditions with Pediarix

Scenario 2 considers a pediatric vaccine market in which Pediarix is available. This scenario reflects actual conditions in the market prior to the licensing of Pentacel on 23 June 2008. As in Scenario 1, the vaccine selection algorithm enables construction of the lowest overall cost formulary for a fixed cost of an injection, across the specified range of values for the cost of an injection. The Scenario 2 results (Table 3.4) indicate the presence of two lowest overall cost formularies. The Monovalent+TriHIBit Formulary is the lowest overall cost formulary for $C \in [\$6.00, \$6.62]$. Since the make-up of the Monovalent+TriHIBit Formulary was detailed in Scenario 1, it is not repeated here. Recall from Scenario 1 though that Sanofi Pasteur earns \$99.85 per child completing the RCIS using this formulary, compared to \$56.75 for GlaxoSmithKline and \$22.58 for Merck.

The 2-shot Pediarix Dominant Formulary is the lowest cost formulary for $C \in [\$6.62, \$14.00]$. This formulary is so named because its backbone is the two injections of Pediarix at the month 2 and month 6 time periods. It supplants the Monovalent+TriHIBit Formulary as the lowest overall cost formulary at a cost of an injection of \$6.62. The COMVAX Dominant Formulary never achieves lowest overall cost status in Scenario 2 however, since Pediarix is priced such that it enters the lowest overall cost formulary \$0.89 ahead of COMVAX in terms of cost of an injection (\$7.51 versus \$6.62). This means that GlaxoSmithKline effectively prices COMVAX out of the market, which explains the decreased sales volume of COMVAX [1]. Since Pediarix does not contain Hib, its natural partner is Merck's Hib. In fact, Merck keeps its two injections of Hib in the 2-shot Pediarix Dominant Formulary. GlaxoSmithKline replaces its own two monovalent HepB injections at the month 2 and month 6 time periods with doses of Pediarix. The economic viability of Pediarix allows

Table 3.4: Lowest overall cost formulary with associated pharmaceutical company revenue per child earned (Scenarios 2 and 3)

Monovalent + TriHIBit® Formulary					2-shot Pediarix® Dominant Formulary			
Cost of injection interval			$ 6.00	$ 6.62	Cost of an Injection interval		$ 6.62	$ 14.00
Pharmaceutical Company	Time Period	Vaccine	Revenue		Vaccine	Notes	Revenue	
Merck	Birth	-			-			
	Month 2	Hib	$ 11.29		Hib		$ 11.29	
	Month 4	Hib	$ 11.29		Hib		$ 11.29	
	Month 6	-			-			
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	-		$ 22.58	-			$ 22.58
GlaxoSmithKline	Birth	HepB	$ 9.75		HepB		$ 9.75	
	Month 2	DTaP, HepB	$ 16.63		**DTaP-HepB-IPV**	HepB exits	$ 48.75	
	Month 4	DTaP	$ 6.88		DTaP		$ 13.75	
	Month 6	DTaP, HepB	$ 16.63		**DTaP-HepB-IPV**	HepB exits	$ 48.75	
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	DTaP	$ 6.88	$ 56.75	DTaP		$ 6.88	$ 127.88
Sanofi Pasteur	Birth	-			-			
	Month 2	DTaP, IPV	$ 18.14		-	DTaP, IPV exit		
	Month 4	DTaP, IPV	$ 18.14		IPV	DTaP exits	$ 11.51	
	Month 6	DTaP, IPV	$ 18.14		-	DTaP, IPV exit		
	Month 12-18	DTaP/Hib	$ 27.31		DTaP/Hib		$ 27.31	
	Month 19-36	-			-			
	Month 48-72	DTaP, IPV	$ 18.14	$ 99.85	DTaP, IPV		$ 18.14	$ 56.96

GlaxoSmithKline to take the DTaP doses away from Sanofi Pasteur in addition to retaining its HepB doses. This market gain is effectively realized due to the economic effectiveness of replacing three injections with a single injection, saving twice the cost of an injection. The use of Pediarix at the month 2 and month 6 time periods forces the month 4 dose of DTaP to be a GlaxoSmithKline product, due to the DTaP manufacturing matching requirement for the months 2, 4, and 6 period series, even though the Sanofi Pasteur DTaP monovalent is equally expensive. Note that the vaccine selection algorithm recognizes that a third dose of Pediarix used at the month 4 time period is wasteful since the RCIS does not call for a HepB dose at that time period. The intrinsic price premium of Pediarix is too expensive to warrant the replacement of only the monovalent DTaP and IPV injections for the more expensive Pediarix. The 3-shot Pediarix Dominant Formulary gives a Pediarix injection at the month 4 period, resulting in the extraimmunization of HepB (which is allowed), but is only economical at higher cost of an injection values. As for Sanofi Pasteur, it loses doses because of Pediarix. All three Sanofi Pasteur DTaP doses for which Pediarix competes are lost, as are the two doses of IPV that Pediarix covers. Sanofi Pasteur only retains the IPV monovalent injection in the month 4 period. Sanofi Pasteur loses revenue but retains a respectable $56.96 of revenue per child, whereas GlaxoSmithKline increases its revenue to $127.88 per child. Merck remains constant at $22.58 per child.

As with Scenario 1, the second formulary has the most impact on the ERPC for the three com-

peting pharmaceutical companies. The 2-shot Pediarix Dominant Formulary is the lowest overall cost formulary for $C \in [\$6.62, \$14.00]$. This means that approximately 98.8% of the customers who value the cost of an injection as represented by a triangular(6,10,14) prefer the 2-shot Pediarix Dominant Formulary to serve as their lowest overall cost formulary. Again the ERPC for the three competing pharmaceutical companies is computed using Equation (3.1). Due to the presence of GlaxoSmithKline's Pediarix, both Sanofi Pasteur and Merck lose ERPC; GlaxoSmithKline obtains 61% of the ERPC, Sanofi Pasteur 28%, and Merck 11%. The value of Pediarix to GlaxoSmithKline can be computed by examining GlaxoSmithKline's ERPC both with and without Pediarix. From such an analysis, Pediarix provides a net gain of \$127.02 - \$47.69 = \$79.33 of ERPC, which means that GlaxoSmithKline can expect to earn \$79.33 more revenue for every child fully completing the RCIS due to its offering of Pediarix. Both Sanofi Pasteur and Merck lose revenue not only due to Pediarix being available, but also to its adroit pricing.

On 23 June 2008, Pentacel was licensed by the FDA for use in the United States pediatric vaccine market. By design, Pentacel competes directly with Pediarix, offering three vaccines in one injection, similar to Pediarix, albeit with different antigens. Scenario 3 examines market conditions with Pentacel priced at its initial federal contract price (ending 31 March 2010) of \$51.49 per dose.

3.2.3 Market Conditions with both Pediarix and Pentacel

Scenario 3 considers a pediatric vaccine market in which both Pediarix and Pentacel are available. This scenario reflects current conditions in the market with vaccine prices set according to the federal contract prices ending 31 March 2010. As in prior scenarios, the vaccine selection algorithm enables construction of the lowest overall cost formulary for a fixed cost of an injection, across the specified range of values for the cost of an injection. The cost of an injection parameters remain the same, as do the vaccines and their associated costs (see Table 3.2).

Scenario 3 results are identical to Scenario 2 results. This means that when Sanofi Pasteur prices Pentacel at \$51.49 per dose, Pentacel never enters the lowest overall cost formulary, even when the cost of an injection is \$14.00, its highest value. Indeed, increasing the cost of an injection to \$20.00 still results in the exclusion of Pentacel from the lowest overall cost formulary. Introducing Pentacel to the pediatric vaccine market at \$51.49 per dose does not increase Sanofi Pasteur's ERPC; it remains at \$57.47, implying a value of zero for Pentacel. A closer examination of Scenario 3 indicates that the 3-shot Pentacel Dominant Formulary overcomes the 2-shot Pediarix Dominant

Formulary at a cost of an injection of $28.88. Moreover, the 3-shot Pediarix Dominant Formulary dominates the 3-shot Pentacel Dominant Formulary (with Pediarix priced at $48.75 per dose and Pentacel priced at $51.49 per dose) independent of the cost of an injection. Based on federal contract prices ending 31 March 2010, to overcome the 3-shot Pediarix Dominant Formulary, Pentacel must be priced no more than $1.03 per dose higher than Pediarix.

These results indicate that at $51.49 per dose (with Pediarix at $48.75 per dose), Pentacel is overpriced. The potential implication of this analysis is that Pentacel is likely to penetrate the pediatric vaccine market very slowly. Essentially, unless the price of Pentacel is aggressively lowered from its initial offering price, there appears no incentive for healthcare system decision-makers to build their formularies with Pentacel as the backbone. Healthcare program administrators with limited budgets are able to complete more RCISs, and hence, fully immunize more children using formularies with Pediarix as its backbone (if the cost of an injection is believed to vary at higher ranges) or even the monovalent-only formulary (if the cost of an injection is believed to vary at lower ranges). Obviously, after a substantial financial investment in the development and licensing of Pentacel an ineffective pricing strategy with the subsequent poor revenue generation is undesirable. One would expect to see a Pentacel price adjustment downward for the next contract cycle (federal contract prices ending 31 March 2011). An adroit question to ask is: how should Sanofi Pasteur determine its price for Pentacel? Scenario 4 addresses this question.

3.2.4 Pricing Pentacel to Maximize Expected Revenue Per Child

Scenario 4 considers a pricing strategy for Pentacel whereby Sanofi Pasteur prices Pentacel under current market conditions (federal contract prices ending 31 March 2010) in order to maximize its ERPC. Pentacel is priced using the MERPC pricing approach (see Equation (3.2)). Sanofi Pasteur's ERPC is then compared to the results reported in Scenario 3 with Pentacel priced at its current $51.49 per dose. As with Scenarios 1-3, the vaccine selection algorithm enables construction of the lowest overall cost formulary for a fixed cost of an injection, across the specified range of values for the cost of an injection. The cost of an injection parameters remain the same, as do the vaccines and their associated costs (listed in Table 3.2). Lastly, the price of Pentacel is not fixed, and is repeatedly adjusted using the MERPC approach to find the price at which Sanofi Pasteur's maximum ERPC is obtained. Implementation of the MERPC approach (as discussed in Section 2) results in an optimal Pentacel price of $44.07 per dose, with Sanofi Pasteur achieving a

Table 3.5: Lowest overall cost formulary with associated pharmaceutical company revenue per child earned (Scenario 4)

Monovalent + TriHIBit® Formulary					3-shot Pentacel® Dominant Formulary			
Cost of injection interval			$ 6.00	$ 6.62	Cost of an Injection interval		$ 6.62	$ 14.00
Pharmaceutical Company	Time Period	Vaccine	Revenue		Vaccine	Notes	Revenue	
Merck	Birth	-			-			
	Month 2	Hib	$ 11.29		-	Hib exits		
	Month 4	Hib	$ 11.29		-	Hib exits		
	Month 6	-			-			
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	-		$ 22.58	-			$ -
GlaxoSmithKline	Birth	HepB	$ 9.75		HepB		$ 9.75	
	Month 2	DTaP, HepB	$ 16.63		HepB	DTaP exits	$ 9.75	
	Month 4	DTaP	$ 6.88		-	DTaP exits		
	Month 6	DTaP, HepB	$ 16.63		HepB	DTaP exits	$ 9.75	
	Month 12-18	-			-			
	Month 19-36	-			-			
	Month 48-72	DTaP	$ 6.88	$ 56.75	DTaP		$ 6.88	$ 36.13
Sanofi Pasteur	Birth	-			-			
	Month 2	DTaP, IPV	$ 18.14		**DTaP-IPV/Hib**	DTaP, IPV exit	$ 44.07	
	Month 4	DTaP, IPV	$ 18.14		**DTaP-IPV/Hib**	DTaP, IPV exit	$ 44.07	
	Month 6	DTaP, IPV	$ 18.14		**DTaP-IPV/Hib**	DTaP, IPV exit	$ 44.07	
	Month 12-18	DTaP/Hib	$ 27.31		DTaP/Hib		$ 27.31	
	Month 19-36	-			-			
	Month 48-72	DTaP, IPV	$ 18.14	$ 99.85	DTaP, IPV		$ 18.14	$ 177.66

maximum ERPC of \$176.72, and GlaxoSmithKline earning an ERPC of \$36.37 (due mostly to its HepB monovalent) while Merck is nearly completely shut out with an ERPC of \$0.27.

The Scenario 4 results (Table 3.5) indicate the presence of two lowest overall cost formularies. As with Scenarios 1-3, the Monovalent+TriHIBit Formulary is the lowest overall cost formulary for $C \in [\$6.00, \$6.62]$. The Monovalent+TriHIBit Formulary was detailed in Scenario 1 and is not repeated here. However, recall from Scenario 1 that Sanofi Pasteur earns \$99.85 per child completing the RCIS using this formulary, compared to \$56.75 for GlaxoSmithKline and \$22.58 for Merck.

The 3-shot Pentacel Dominant Formulary is the lowest cost formulary for $C \in [\$6.62, \$14.00]$. This formulary is so named because the backbone of the formulary is the three injections of Pentacel at the month 2, 4, and 6 time periods. It supplants the Monovalent+TriHIBit Formulary as lowest overall cost at a cost of injection of \$6.62. The Monovalent+TriHIBit Formulary moves from lowest overall cost formulary to third best at a cost of an injection of \$6.62. The 2-shot Pediarix Dominant formulary, which would have become the lowest overall cost formulary at a cost of injection of \$6.62, becomes the second best formulary. The MERPC approach selects a price of \$44.07 per dose for Pentacel, resulting in Sanofi Pasteur effectively pricing Pediarix entirely out of the market. When Pentacel is present in the lowest overall cost formulary, Merck's Hib is not selected. In regard to HepB, GlaxoSmithKline's monovalent is less expensive than Merck's,

resulting in no Merck vaccines in the lowest overall cost formulary. GlaxoSmithKline retains only its three HepB monovalent injections (and half a DTaP dose in the month 48-72 period) from the Monovalent+TriHIBit Formulary. When compared to the 2-shot Pediarix Dominant Formulary, GlaxoSmithKline loses its two doses of Pediarix in the month 2 and month 6 periods and the DTaP monovalent dose in the month 4 period. The three doses of HepB remain, as its HepB monovalent is less expensive than Merck's HepB. The effective pricing of Pentacel allows Sanofi Pasteur to obtain the doses for DTaP, Hib, and IPV for the month 2, 4, and 6 doses. From the Monovalent+TriHIBit Formulary, Sanofi Pasteur replaces its own DTaP and IPV monovalents as well as Merck's two Hib injections. From the 2-shot Pediarix Dominant Formulary, Sanofi Pasteur replaces the DTaP and IPV from Pediarix in months 2 and 6 and the GlaxoSmithKline DTaP monovalent in month 4 as well. In the 3-shot Pentacel Dominant Formulary (see Table 3.5), Sanofi Pasteur earns \$177.66 of revenue per child, whereas GlaxoSmithKline loses nearly 72% of the revenue it earns with the 2-shot Pediarix Dominant Formulary (\$127.88 per child) at \$36.13 of revenue per child. Merck earns no revenue in the 3-shot Pentacel Dominant Formulary.

The 3-shot Pentacel Dominant Formulary is the lowest cost formulary for $C \in$ [\$6.62,\$14.00] which is approximately 98.8% of the probability density of the chosen distribution for cost of injection. This means that approximately 98.8% of the customers who value the cost of an injection as represented by a triangular(6,10,14) prefer the 3-shot Pentacel Dominant Formulary to serve as their lowest overall cost formulary. The ERPC for the three competing pharmaceutical companies is computed using (1). Due to the presence of Sanofi Pasteur's appropriately priced Pentacel, both GlaxoSmithKline and Merck lose ERPC when compared to the results from Scenario 3. In particular, Sanofi Pasteur obtains 83% of the ERPC, while GlaxoSmithKline obtains 17%, and Merck obtains slightly above 0%. The value of Pentacel is computed by comparing Sanofi Pasteur's ERPC with Pentacel priced at its current \$51.49 per dose to its ERPC with Pentacel priced at \$44.07 per dose. It follows that Pentacel provides a net gain of \$119.25 for its ERPC. This means that Sanofi Pasteur can expect to earn \$119.25 more revenue for every child fully completing the RCIS by adjusting downward the price of Pentacel. The MERPC approach provides a more effective price for Pentacel, resulting in Sanofi Pasteur increasing its relative contribution to the total ERPC from 28% to 83%. An aggressively re-priced Pentacel provides incentive for healthcare system decision makers to order pediatric vaccine formularies with Pentacel as its backbone. If priced at \$44.07 per dose, one would expect to see substantial revenue growth for Pentacel.

3.3 Conclusions

This chapter describes a methodology for analyzing and assessing pricing strategies for pediatric combination vaccines and their impact on the United States pediatric vaccine market. An analysis of three pediatric vaccine markets featuring both Pediarix and Pentacel is presented whereby a comparison of pharmaceutical company expected revenue provides a measure of value for the combination vaccines. Secondly, an approach is given for pricing a pediatric vaccine to ensure that a pharmaceutical company achieves its highest possible ERPC. These analyses provide insight into how Pediarix and Pentacel impact the United States pediatric vaccine market.

Operations research techniques have been used to assess the value, long term market prospects, and potential pricing strategies for two combination vaccines, Pediarix and Pentacel. As the complexity of the RCIS increases, pharmaceutical companies will respond with new combination vaccines. As these new combination vaccines gain FDA approval and enter the market, the methodology reported in this chapter provides a valuable resource for pediatric vaccine purchasers and suppliers alike to determine the price premium intrinsic to such vaccines.

Several potentially important economic factors that could impact the overall cost of immunization are not included in this study. The exclusion of such factors is due primarily to the lack of data or economic models regarding them. Some factors are important as an issue of differentiation between manufacturer products. For example, vaccine efficacy, adverse reaction frequency, shelf life, and thermal storage requirements [31] could all be factors distinguishing two vaccines and may influence the decision on which product to purchase. In addition to product differentiation, this study does not address potential cost savings associated with reduced inventory handling resulting from the reduction in the number of separate vaccines included in the lowest overall cost formulary. Lastly, brand loyalty, volume discounting, risk of shortages, and formulary inertia are not addressed due to the difficulty in quantifying economic model parameters describing them.

The results presented here should interest those within the pediatric healthcare community seeking information regarding the relative economic value, effective pricing strategies, and impact of combination vaccines on market conditions. A combination vaccine holds an intrinsic price premium based on the sum of its individual vaccine components and relates directly to how a particular segment of the market values the cost of an injection. It behooves both the pharmaceutical companies and purchasers to arrive at a fair market price in order for beneficial transactions to occur. A cursory examination of the portion of the pediatric vaccine market (in terms of volume and value)

that is captured in the federal contract prices provides insight into the overall applicability of the results of the analysis to the market. For a population of approximately 4.3 million children requiring immunization annually [14], approximately 77.4% achieve full immunization coverage [10]; and of those, approximately 43% are immunized via the Vaccines For Children program using pediatric vaccines bought at federal contract prices [7]. This is a lower bound on the volume of pediatric vaccines bought at federal contract prices (since federal 317 funds and state funds also use federal contract prices, increasing the volume above 43%). Using only monovalents, it costs a minimum of $626.00 to complete the RCIS (excluding Rotavirurs, Influenza, Hepatitis A, and Meningococcal) for each child, at federal contract pricing, while it costs $949.13 using private sector prices. This implies that as a lower bound, the portion of the market captured in the prices that the CDC negotiates is approximately 33% with respect to value. In a related issue, an examination of the potential economic consequences of an improper pricing strategy for Sanofi Pasteur's Pentacel reveals a $170M per year difference in expected revenue. Such a value is calculated using population and vaccine coverage data from the Central Intelligence Agency [14] and CDC [10, 7], in conjunction with the computed $119.25 value of a properly priced Pentacel (see Section 3.2.4).

The analysis of Pediarix and Pentacel presented provides a new approach to understanding the impact of pricing on pediatric vaccine markets. By design, both these combination vaccines cannot be present in the same vaccine formulary. The natural market tendency will be to gravitate towards the combination vaccine that provides the best economic value. The pricing strategy for each vaccine and the belief regarding the distribution of the cost of an injection both significantly impact the purchasing choice. The pricing strategy suggested (MERPC) indicates an aggressive under pricing of Pentacel is necessary to increase its expected revenue. Yet, Pediarix could implement a similar strategy. Such a Bertrand Duopoly price competition results in short term savings for vaccine purchasers. However, such a situation may lead to competing pharmaceutical companies exiting the pediatric vaccine market, resulting in a vaccine monopoly that leads to larger price increases in the long term. It is in the interest of both the pharmaceutical industry and vaccine purchasers to pursue a healthy economic relationship in the interests of long term market stability. It will also be interesting to observe how GlaxoSmithKline and Sanofi Pasteur adjust their prices for Pediarix and Pentacel, respectively, over the next several years, as the each wrestle to gain and secure revenue for their products.

CHAPTER 4

THE WEIGHTED SET COVERING GAME: A BERTRAND OLIGOPOLY PRICING MODEL

This chapter explores a generalization of the classical Bertrand model. The proposed Bertrand oligopoly pricing model, in the form of a static strategic game, characterizes interactions between asymmetric firms in a homogeneous multiple product market with a combinatorial and interdependent demand structure. A firm controls a given collection of bundles containing one or more products and must determine the price for each of its bundles so as to maximize profit.

Consumer demand behavior is characterized by a WSC optimization problem in which a consumer seeks to obtain at least one of each of the products (at a minimum overall cost) by purchasing bundles of the products. The model employs a smooth, concave demand curve to capture consumer price sensitivity to total cost, with the notable characteristic that the consumer is sensitive only to the aggregate price of the lowest overall cost set of bundles, not the individual prices of the bundles. The firms face constant returns, in that each firm has only a constant marginal cost of production to consider. As is typical of Bertrand models, assume that each firm simultaneously (and independently) chooses the prices of its bundles of products and has the capacity to supply all forthcoming demand. The game is static, in that the firms anticipate playing the game only once. A no-bankruptcy constraint is also imposed, in that no bundle is priced below its marginal cost.

The chapter is organized as follows: Section 4.1 provides a description of the proposed oligopoly pricing models and states the main Nash equilibrium existence results. Section 4.2 describes the computational difficulty of computing Nash equilibria for the weighted set covering game and introduces an iterative improvement algorithm devised to compute such equilibria. Section 4.3 provides proofs of the conditions required for the existence of Nash equilibria. Section 4.4 demonstrates the utility of two games by applying them to the analysis of the United States public sector pediatric vaccine market. Section 4.5 provides concluding comments and directions for future research.

4.1 The Games

This section describes the oligopoly pricing models formulated to characterize oligopolistic interactions between asymmetric firms in a homogeneous multiple product market. Several factors complicate such interactions, most notably the specification of demand from the solution to an integer program (IP). Analysis indicates that a pure strategy Nash equilibrium for the weighted set covering game always exists. The repeated game version of the model relaxes the static game's temporal assumption of only one interaction, enabling repeated interactions between the firms. Conditions for the existence of a sub-game perfect Nash equilibrium in the repeated game are presented.

4.1.1 The Weighted Set Covering Game

This section describes the weighted set covering game, a Bertrand oligopoly pricing model. Consider a simultaneous move, single stage, complete information game. The simplest way to portray the game is in an appended strategic form, consisting of five key parts: the set of players (firms), the appended game structure (i.e., the WSC optimization problem), the manner in which players interact with the appended game structure, the set of strategies (prices) available to each player, and the manner in which the players' payoffs (profits) depend on the strategies chosen. Each firm attempts to maximize its profits by independently selecting an appropriate pricing strategy, knowing only the structure of the game (i.e., firms are rational and intelligent). Thus, each firm must consider the pricing strategies that the other firms are likely to select. Moreover, in oligopoly pricing models such as the one reported in this study, important elements in the determination of each firm's profits are the relevant market demand structure and its own cost structure [59]. Several definitions are required to precisely describe the game.

Let N denote the set of firms in the market. Firms produce a collection of bundles containing one or more homogeneous products. Homogeneous products originating from different firms are perceived as identical products by consumers; when appropriate, an additional marginal cost component is included to account for minor product differentiation. The aggregate collection of all of the firms' bundles allows characterization of the market demand structure.

There is no direct characterization of demand. A WSC optimization problem describes market demand with respect to a single consumer, where S is the set of homogeneous products and B, a set of subsets of S, is the set of bundles of products available for purchase from the firms in N. A

rational consumer seeks to obtain at least one of every homogeneous product in S at the lowest possible overall cost by purchasing bundles in B (i.e., a consumer seeks to find a minimum cost collection C of bundles from B such that C covers all elements in S). The minimum weighted cover, C, ensures $\bigcup_{j \in C}\{j\} \supseteq S$ at overall minimum cost. The collection of restricted covers, R, contains covers deemed infeasible as a solution. In the algorithm introduced in section 4.2, R is used in conjunction with binary cuts [2] to derive alternative optimal solutions. In this chapter, the defining WSC optimization problem is parameterized by $W = (S, B, (w_j)_{j \in B}, (\tilde{c}_j)_{j \in B}, \tau, R)$ and is modeled as a 0-1 IP:

$$
\begin{array}{lllll}
\text{WSC}(W) & & & & \\
\text{Minimize} & \displaystyle\sum_{j \in B} (w_j + \tilde{c}_j + \tau)\, x_j & & & \\
\text{subject to} & \displaystyle\sum_{j \in B} a_{ij} x_j & \geq & 1 & \text{for all } i \in S, \\
& x_j & \in & \{0,1\} & \text{for all } j \in B, \\
& \displaystyle\sum_{j \in \hat{C}} x_j - \sum_{j \notin \hat{C}} x_j & \leq & \left|\hat{C}\right| - 1 & \text{for all } \hat{C} \in R,
\end{array}
$$

where,

w_j is the price corresponding to bundle $j \in B$,

$\tilde{c}_j \geq 0$ is the product differentiation price adjustment to bundle $j \in B$,

$\tau \geq 0$ is a penalty cost for including a bundle in cover $C \subseteq B$,

$a_{ij} = 1(0)$ if product $i \in S$ is in bundle $j \in B$, $(j \notin B)$, and

$x_j = 1(0)$ indicates bundle $j \in C$, $(j \notin C)$.

To capture the relationship between firms and the bundles of products produced by them, define the set valued map $g : N \to B$, where $g(f) \subseteq B$ is the set of bundles produced by firm $f \in N$. Define

$$K_f = \prod_{j \in g(f)} K_j$$

as the Cartesian product set of prices available to each firm f, where $K_j = \{w_j \in \Re \mid c_j \leq w_j \leq \beta_j\}$ is the closed interval of available prices for a bundle of products $j \in g(f)$. The weight w_j represents the price specified by firm f for bundle $j \in g(f)$. Each bundle j has a constant marginal cost of production c_j and an upper bound in price of β_j such that $0 \leq c_j \leq \beta_j$. A no-bankruptcy assumption prevents the pricing of a bundle under its marginal cost. By design, the set of prices is

compact and convex.

When the game is played, each firm f must simultaneously select one of the pricing tuples in the set K_f (i.e., each firm must select a feasible price for each of its bundles). The combination of bundle prices that the firms in N collectively select is referred to as a *price point*, $\mathbf{w} = (w_j)_{j \in B}$. The set of prices available to any firm f may differ from the set of prices available to any firm i due to possibly different cost structures or upper bounds on the set of available prices. When the collection of bundles produced by any two firms differ or their respective cost structures differ, the game is considered asymmetric.

The solution to WSC(W) depicts consumer demand behavior given the market conditions described by W. With the exception of the price point $\mathbf{w}$ and the set of restricted covers R, the market conditions depicted by W remain unchanged. Thus, the market conditions are often described only by the price point $\mathbf{w}$ with R empty, unless otherwise noted. Let the minimum weighted set cover C denote the solution to WSC(W) and let $z(\mathbf{w}) = \sum_{j \in C} (w_j + \tilde{c}_j + \tau) x_j$ denote the associated overall cost of C. Define $X(\mathbf{w})$ as the collection of all minimum weighted covers available at the price point $\mathbf{w}$. $X(\mathbf{w})$ enables specification of the market share for each bundle (i.e., how many of each bundle is purchased per customer). Define $\psi_j = \frac{\sum_{C \in X(\mathbf{w})} I_{C_j}}{|X(\mathbf{w})|} \in [0, 1]$ as the market share of bundle $j \in B$ at the market conditions described by W, where $I_{C_j} = 1(0)$ if bundle $j \in (\notin) C \in X(\mathbf{w})$. Assume that when there is more than one optimal cover, demand is shared equally among the optimal covers.

The aggregate market demand function $D : \Re \to \Re$ specifies the total quantity of bundles purchased as a function of the overall cost of the minimum weighted cover and is of the form:

$$D(z(\mathbf{w})) = d - \eta (z(\mathbf{w}))^{\lambda}, \tag{4.1}$$

where D is assumed to be twice continuously differentiable and concave (i.e., $\frac{d^2 D}{dz^2} \leq 0$). This form enables specification of conventional demand functions typically found in the literature [58, 59].

To complete the description of the game, denote the payoff function of each firm $f \in N$ as:

$$\pi_f(\mathbf{w}) = D(z(\mathbf{w})) \sum_{j \in g(f)} (\psi_j(\mathbf{w}) (w_j - c_j)). \tag{4.2}$$

Each firm f receives the sum of the unit profits for each bundle $j \in g(f)$ present in each cover $C \in X(\mathbf{w})$ times the number of covers purchased by consumers. In the case where multiple optimal

covers are available (i.e., $|X(\mathbf{w})| > 1$), the market share of a particular bundle is determined by the number of optimal covers in $X(\mathbf{w})$ in which it is present. For example, if $X(\mathbf{w}) = \{\{1,2\},\{2,3\}\}$ and $D(z(\mathbf{w})) = 100$, then $\psi_1 = 0.5$, $\psi_2 = 1.0$, and $\psi_3 = 0.5$, resulting in a demand of 50, 100, and 50 for bundles 1, 2, and 3, respectively.

Formally, the *Weighted Set Covering Game* is any Γ of the form

$$\Gamma = (N, W, g(N), (K_f)_{f \in N}, (\pi_f)_{f \in N}).$$

The game theoretic solution to Γ is now examined. Analysis reveals insights regarding long term market profit prospects that are important to both consumers and firms. Solution concepts in the study of games differ mostly with respect to the level of collusion or cooperation allowed between firms [41]. In this study, for the pure strategy Nash equilibrium sought in Γ, no cooperation is allowed.

As Vives [59] notes, in most situations typifying economic conflict, two or more firms make decisions that influence each other's profits, while operating in a market environment in which binding legal contracts may not be enforceable (e.g., anti-trust laws). In such situations, noncooperative game theory provides an appropriate mathematical framework for analysis, as it enables the determination of a rational prediction regarding the outcome of the game.

Nash's concept of equilibrium [43] is the central solution concept in noncooperative game theory and consequently, to the study of oligopoly pricing models [59]. A Nash equilibrium (Definition 1) is a set of pricing strategies (i.e., a price point) such that no firm can unilaterally deviate from its strategy in order to realize a gain in profits.

Definition 1 (Nash Equilibrium)**.** *In Γ, a price point $\mathbf{w}^* = \left(\mathbf{w}_f^*; \mathbf{w}_{-f}^*\right)$ constitutes a pure strategy Nash equilibrium if for any firm $f \in N$, $\pi_f\left(\mathbf{w}_f^*; \mathbf{w}_{-f}^*\right) \geq \pi_f\left(\mathbf{w}_f; \mathbf{w}_{-f}^*\right)$, for all other price points $\mathbf{w}_f$, where $\mathbf{w}_f^* \in K_f$ denotes the set of bundle prices controlled by firm f, and $\mathbf{w}_{-f}^* \in K_{-f}$ denotes the set of bundle prices controlled by firms other than f.*

When attempting to predict or stipulate firms' pricing behavior in a game, the price point suggested must be a Nash equilibrium; if the suggested price point is not a Nash equilibrium, *irrational* behavior is being attributed to at least one of the firms, in that it could change its pricing strategy to increase its profits but is choosing not to do so. Nash's equilibrium provides a consistent solution concept [59] in that all firms behave rationally; a nonequilibrium specification

is self-defeating, since a firm can gain by changing its pricing strategy. Moreover, any solution concept imputing systemic irrational behavior to players in a game warrants clear justification.

Determining the existence of Nash equilibria and efficiently computing them are important areas of research (see for example [44, 47, 52]). While most studies concentrate on mixed strategy Nash equilibria, this effort focuses on pure strategy Nash equilibria. Unfortunately, as Vives [59] notes, "Nonexistence of Nash equilibria in pure strategies is pervasive in oligopoly models." Note that Nash equilibria in this chapter refer only to pure strategy Nash equilibria.

Γ is a game with infinite strategy spaces and models a strategic economic situation in which firms may choose prices from a continuum of prices. As with Bertrand's classic game [3], Γ exhibits discontinuities in the firms' payoffs. For example, when determining demand for the simple case in which a single homogeneous product is produced by two firms and both products are equally priced, the tie must be broken according to some predetermined sharing rule. This rule ultimately leads to a discontinuity in the firms' payoffs since one firm's slight decrease in the price of the product results in it obtaining full market demand, a discontinuous increase when compared to the demand it received when prices were equal.

As a consequence of the discontinuous nature of Γ, standard theorems found in the literature (see for example, [16, 17, 26, 43]) cannot be applied to establish the existence of pure strategy Nash equilibria. However, using the algorithm detailed in Section 4.2, pure strategy Nash equilibria (some in the limiting sense) can always be constructed. The following theorem states the main result, proven in Section 4.3.

Theorem 1 (Static Game Equilibrium Existence)**.** *Given an instance of* Γ*, a pure strategy Nash equilibrium always exists.*

In the results presented in this chapter, a pure strategy Nash equilibrium can exist in the limiting sense. This concept merits further discussion. Consider an open set problem as discussed by Tirole [58]. To illustrate, consider a Bertrand duopoly in which two firms face a price competition with asymmetric costs, where $\hat{c}_1 < \hat{c}_2$, over the sale of a single homogeneous good. If the monopoly price is greater than or equal to the second firm's cost, then the optimal price for the first firm does not exist in a strict sense because the first firm will always be better off by setting its price ever closer to $\hat{c}_2$. Therefore, in such situations, an equilibrium in the limiting sense is a price point $(\hat{p}_1 = \hat{c}_2, \hat{p}_2 = \hat{c}_2)$ where the first firm sets its price $\hat{p}_1$ equal to the second firm's cost and receives the entire market demand, earning a unit profit of $\hat{c}_2 - \hat{c}_1$ and where the second firm sets its price

$\hat{p}_2$ as low as possible, at its own unit cost, receives no demand, and earns no profit.

In Γ, the concept of an equilibrium in the limiting sense allows a firm with an absolute advantage to increase the cost of a lowest overall cost cover up to the cost of the next lowest cost cover. The next lowest cost cover receives no demand and the firms whose bundles are present in the next lowest cost cover earn no profit from its sale.

4.1.2 The Repeated Weighted Set Covering Game

This section introduces the repeated weighted set covering game, the analysis of which addresses the often problematic temporal assumption in Γ of a single economic interaction between firms. In reality, firms are likely to interact repeatedly in the market of interest. Adoption of a repeated game structure enables exploration of more sustainable and higher profit price points. As Myerson [41] notes, firms in the same market may behave quite differently toward one another when there is an expectation of a long-term relationship involving repeated interaction. In the classic symmetric Bertrand game, the Nash equilibrium provides zero economic profit for the competing firms. In such a situation, firms would like to transform the game and extend the set of Nash equilibria to include the higher profit results [41, 58].

In a repeated game, a firm must consider the effect of its current pricing strategy on the pricing strategies of other firms in the future and the attendant impact on its own future profits. Such considerations almost certainly lead to more cooperative behavior, assuming the firms value future profits highly enough. The temporal extension to Γ enables examination of tacit collusion in the market and its effect on profits and costs for the firms and consumers involved, respectively. Interestingly, the possibility of tacit collusion is entirely enabled by a noncooperative game theoretic mechanism.

Consider the repeated weighted set covering game with standard information, where the exact same instance of Γ is replicated an infinite number of times. Several definitions are required to precisely describe the repeated game.

Define $\pi_f(\mathbf{w}^{(t)})$ as firm f's profit for time period t, where $t = \{0, 1, \ldots\}$, with the bundles of products in B priced at $\mathbf{w}^{(t)}$. In Γ^r, firm f wants to maximize the δ-discounted average of its profits,

$$(1 - \delta_f) \sum_{t=1}^{\infty} \delta_f^{t-1} \pi_f(\mathbf{w}^{(t)}), \tag{4.3}$$

where $\pi_f(\mathbf{w}^{(t)})$ is determined according to (4.2) and $\delta_f \in [0,1)$ is the discount factor, a measure of the patience or long-term financial perspective of firm f. By design, δ_f close to one represents a patient firm, one that values future profits relatively high with respect to current profits. δ_f can also represent an alternative source of profit for firm f, with the payoffs earned at each replication of Γ^r (i.e., $\delta_f \equiv \frac{1}{1+r}$, where r is the interest rate for a single time period).

At each time period t, the firms in N simultaneously select prices for the current Γ replication. Each firm's pricing strategy may depend on the history of the prices set in replications prior to t, where a history $H^{(t)} = \left\{\mathbf{w}^{(1)}, \mathbf{w}^{(2)}, \ldots, \mathbf{w}^{(t-1)}\right\}$. Each firm is able to perfectly recall other firms' past pricing decisions. A pricing strategy for firm f, $\sigma_f(H^{(t)}) \in \mathcal{A}_f$, specifies a price $w_j^{(t)}$ for each bundle $j \in g(f)$ for every possible sequence of outcomes $\left\{\mathbf{w}^{(1)}, \mathbf{w}^{(2)}, \ldots, \mathbf{w}^{(t-1)}\right\}$ of Γ^r. A subgame-perfect Nash equilibrium is then sought where for every firm $f \in N$ and any history $H^{(t)}$, the strategy employed by firm f for periods $t, t+1, \ldots$ maximizes (4.3).

Formally, the *Repeated Weighted Set Covering Game* is any Γ^r of the form

$$\Gamma^r = \left(\Gamma, (\mathcal{A}_f)_{f\in N}, H^{(t)}, (\delta_f)_{f\in N}\right).$$

The analysis of Γ^r proceeds by formulating a strategy for each firm $f \in N$ that induces subgame-perfect equilibria with profits greater than those earned in Nash equilibria in Γ. Denote $\mathbf{w}^*$ and π_f^* as a Nash equilibrium price point and corresponding profit for firm f, respectively, in the static game Γ. Consider the following *grim trigger strategy*: let each firm $f \in N$ tacitly agree to a mutually beneficial price point $\hat{\mathbf{w}}$, where at each time period t, firm f charges $(w_j^{(t)})_{j\in g(f)} = (\hat{w}_j)_{j\in g(f)}$ and produces $\psi_j D(z(\mathbf{w}^{(t)}))$ of each bundle $j \in g(f)$. Firm f maintains this collusive agreement provided $(w_j^{(\hat{t})})_{j\in g(-f)} = (\hat{w}_j)_{j\in g(-f)}$ for all $\hat{t} < t$, where $g(-f)$ is the set of bundles in B not controlled by firm f. Otherwise, firm f reverts to Bertrand behavior by setting prices at $(w_j^*)_{j\in g(f)}$ for all time periods beyond t.

More formally, define the grim trigger strategy $\sigma_f(H^{(t)}) \in \mathcal{A}_f$ as

$$\sigma_f\left(H^{(t)}\right) = \begin{cases} (\hat{w}_j)_{j\in g(f)} & \text{if } H^{(t)} \text{ is empty,} \\ (\hat{w}_j)_{j\in g(f)} & \text{if } w_j^{(\hat{t})} = \hat{w}_j,\ j \in g(-f),\ \text{for all } \hat{t} < t, \\ (w_j^*)_{j\in g(f)} & \text{otherwise.} \end{cases}$$

Under the grim trigger strategy, a firm $f \in N$ selects high prices and receives a higher profit than

is achieved should it and the other firms engage in Bertrand behavior. Cooperation is maintained until an opposing firm deviates by undercutting in price. When deviating, the opposing firm receives a (possibly substantial) short-term gain in profit but would receive its lower Nash equilibrium profit in all later periods, as firm f responds to the deviation by setting a low Nash equilibrium price *ad infinitum*. Such unforgiving punishment may appear extreme, yet it is the threat of this punitive action that induces cooperative play. There are other less punitive strategies that may induce equilibria. Myerson [41] discusses a variety of strategies in the context of repeated games (e.g. *tit-for-tat*, *getting even*, *limited punishment*, and *mutual punishment*).

In a standard repeated game such as Γ^r, when firms are sufficiently patient, almost any feasible price point can be realized in an equilibrium. In the game theory literature, the theorems proving such results are often referred to as *general feasibility theorems* (see [22, 23, 41, 53]). Fudenberg and Maskin [23] provide a general feasibility theorem for subgame-perfect Nash equilibria of standard repeated games with discounting. In particular, they provide proof that given a collusive agreement stipulating an equilibrium price point at which all firms receive a payoff greater than the payoff they can achieve by acting unilaterally, a discount factor exists that sustains the equilibrium.

In the analysis of Γ^r, examining each firm f's optimal deviation from the stipulated equilibrium price point, $\hat{\mathbf{w}}$, provides the desired conditions on each firm's discount factor, δ_f, necessary for the sustainment of the equilibrium. In order for the collusive agreement to be rational and the grim trigger strategy equilibrium maintained, the short-term gain must be less than or equal to the long-term loss for every firm. The profit stream for maintaining the collusive agreement is $(\pi_f(\hat{\mathbf{w}}), \pi_f(\hat{\mathbf{w}}), \ldots)$, resulting in a discounted average of $\pi_f(\hat{\mathbf{w}})$. The profit stream for deviating for a short term gain is $\left(\pi_f^d, \pi_f^*, \pi_f^*, \ldots\right)$, resulting in a discounted average of $(1-\delta_f)\left(\pi_f^d + \frac{\pi_f^*\delta_f}{1-\delta_f}\right)$, where π_f^d is the maximum profit attainable by firm f should it deviate from $\hat{\mathbf{w}}$. The required conditions necessary for the sustainment of the grim trigger strategy equilibrium is given by,

$$\delta_f \geq \frac{\pi_f^d - \pi_f(\hat{\mathbf{w}})}{\pi_f^d - \pi_f^*}, \text{ for all } f \in N, \tag{4.4}$$

which leads to the main existence result for Γ^r.

Theorem 2 (Repeated Game Equilibrium Existence)**.** *If $(\pi_f(\hat{\mathbf{w}}))_{f\in N}$ Pareto dominates the payoffs $(\pi_f^*)_{f\in N}$ of a Nash equilibrium $\mathbf{w}^*$ of the static game Γ, then, if $\delta_f \geq \frac{\pi_f^d - \pi_f(\hat{\mathbf{w}})}{\pi_f^d - \pi_f^*}$ for all $f \in N$, there exists a subgame-perfect equilibrium of the infinitely repeated game Γ^r, where the δ-discounted average of profits firm f is $\pi_f(\hat{\mathbf{w}})$.*

Proof. The result follows from Fudenberg and Maskin [23] and (4.4). ∎

One can argue that the theory of repeated games is too successful in explaining tacit collusion since it can be used to justify nearly any feasible price point as a Nash equilibrium. Indeed, as Tirole [58] notes, the large set of equilibria is an "embarrassment of riches". In some manner, firms must coordinate on a *focal equilibrium*. How this focal equilibrium is selected remains an important issue. Schelling [54] considered the matter in great detail, arguing that any galvanizing force that focuses the firms' attention on a particular equilibrium point is a *focal effect*, facilitating the selection of that price point (akin to the satisfaction of a self-fulfilling prophecy). Welfare properties of *efficiency* and *equity* may determine the focal equilibria [41]. If only one focal equilibrium exists (due to galvanizing, exogenous focal effects), then one should expect to see it realized.

4.2 The Iterative Improvement Algorithm (IIA)

This section discusses complexity issues concerning Γ and provides a detailed description of the iterative improvement algorithm (IIA) for computing its Nash equilibria. The inherent difficulty in computing a Nash equilibrium is unsurprising, given that the computation of payoffs in Γ involves finding a solution to an intractable problem (i.e., WSC). Consider the following theorem:

Theorem 3. *Given an instance of* Γ*, computing a pure strategy Nash equilibrium is NP-hard.*

Proof. Let $\tilde{S}$, $\tilde{B} = \{\tilde{B}_1, \ldots, \tilde{B}_n\}$, and $(\tilde{w}_j)_{j\in\tilde{B}}$ denote an arbitrary instance of the WSC optimization problem, which is *NP*-hard [24, 32]. Define the corresponding particular instance of Γ as follows: Set $N = \{1, 2, \ldots, n\}$, $W = (S = \tilde{S}, B = \tilde{B}, (w_j) = (\tilde{w}_j)_{j\in\tilde{B}}, (\tilde{c}_j)_{j\in B} = 0, \tau = 0, R = \oslash)$, $(g(f))_{f\in N} = \tilde{B}_f$, $(K_f)_{f\in N} = (\tilde{w}_j)_{j\in g(f)}$, and $(\pi_f)_{f\in N} = 0$. Suppose that there exists a polynomial time algorithm to determine $X(\mathbf{w})$, the collection of minimum weighted covers available at the price point $\mathbf{w}$, given the collection B of bundles of a set S of products. Then, by design, the arbitrary instance of WSC can be solved in polynomial time. In particular, given the Turing reduction from WSC to Γ, $X(\mathbf{w}) = X(\tilde{\mathbf{w}})$ solves the arbitrary instance of the WSC problem defined by $\tilde{S}$, $\tilde{B}$, and $(\tilde{w}_j)_{j\in\tilde{B}}$. Therefore, Γ is *NP*-hard. ∎

IIA seeks a Nash equilibrium price point via a best response scheme, iteratively choosing a firm with the ability to increase its profit, then adjusting prices to achieve the greatest increase in profit (subject to the profit level indicated by the inter-bundle Cournot equilibrium, detailed in step

13). By design, IIA constructs a sequence of price points that must terminate under one of three conditions. Several definitions are needed to describe the algorithm.

A *veto firm* is a firm that controls at least one bundle (not at its price limit) in every lowest overall cost cover and every tight bounding cover.

Definition 2 (Set of Veto Firms)**.** *Given an instance of* Γ *and execution of IIA, the set of veto firms at iteration* k *is defined as* $\Omega^k \equiv \{f \in N :$ *for all* $C \in X \bigcup L^k$ *such that* $\sum_{h \in C} (w_h^k + \tilde{c}_h + \tau) \leq z^k$*, there exists* $j \in g(f) \bigcap C$ *such that* $\beta_j - w_j^k > 0\}$*.*

An *active veto firm* is a veto firm yet to attain the equilibrium profit associated with an inter-bundle Cournot equilibrium price point.

Definition 3 (Set of Active Veto Firms)**.** *Given an instance of* Γ *and execution of IIA, the set of active veto firms at iteration* k *is defined as* $\tilde{\Omega}^k \equiv \left\{ f \in \Omega^k : u_f^k \neq p^* \right\}$ *.*

A *veto bundle* is a bundle $j \in g(n)$ that is a member of at least one cover in X or L^k.

Definition 4 (Set of Veto Bundles)**.** *Given an instance of* Γ *and execution of IIA, the pivot firm's set of veto bundles is defined as* $V \equiv \{j \in g(n) : j \in C,\ C \in X \bigcup L^k\}$*.*

Prior to applying IIA, a preprocessing reduction stage occurs in which equivalent, dominated bundles (see Definition 5) are sequentially removed from consideration.

Definition 5 (Dominated Bundle)**.** *For bundles* $i, j \in B$*,* i *is dominated by* j *if* $i \subseteq j$*,* $j \subseteq i$ *and* $c_i \geq c_j$*.*

Among a set of equivalent bundles, the remaining unique bundle is one with the lowest unit cost and, as part of the process, is bounded in price by the cost of the bundle with the second lowest unit cost. Therefore, a firm will only increase the price of a particular bundle up to the next best price of an equivalent competing bundle. This is due to the results of a simple single homogeneous product n-player Bertrand oligopoly game. After this reduction process, the collection of bundles B in Γ contains only unique bundles.

IIA begins with an initialization phase, consisting of 13 steps.

(Step 1) The iteration counter, k, is set to zero, the initial price point, $\mathbf{w}^k$, is set to $\mathbf{c}$, and the collection of *restricted* covers (i.e., covers imputed as infeasible, and hence, not available as a solution), R, is set to empty.

Algorithm 1 Iterative Improvement Algorithm (IIA)

Require: Instance of Γ
Ensure: $\mathbf{w}^k$ is a Nash equilibrium price point
1: Set $k \leftarrow 0$, $\mathbf{w}^k \leftarrow \mathbf{c}$, and $R \leftarrow \oslash$
2: Solve WSC where $W = (S, B, \mathbf{w}^k, \tilde{\mathbf{c}}, \tau, R)$ to obtain C^* and z^*
3: Set $X \leftarrow C^*$ and $z^k \leftarrow z^*$
4: **repeat**
5: Set $R \leftarrow X$
6: Solve WSC where $W = (S, B, \mathbf{w}^k, \tilde{\mathbf{c}}, \tau, R)$ to obtain C^* and z^*
7: **if** $z^* = z^k$ **then** set $X \leftarrow X \bigcup C^*$
8: **until** $z^* > z^k$
9: Set $L^k \leftarrow C^*$
10: Determine Ω^k
11: **if** Ω^k is empty **then return** $\mathbf{w}^k$
12: Set $(u_f^k \leftarrow 0)_{f \in \Omega^k}$ and $\tilde{\Omega}^k \leftarrow \Omega^k$
13: Solve Equation (4.6) to obtain p^*
14: **repeat**
15: Set $n \leftarrow \min_{i \in \tilde{\Omega}^k} \{i\}$
16: **while** Conditions (i) and (ii) hold **do**
17: Set $R \leftarrow X \bigcup L^k$
18: Solve WSC where $W = (S, B, \mathbf{w}^k, \tilde{\mathbf{c}}, \tau, R)$ to obtain C^* and z^*
19: Set $L^k \leftarrow L^k \bigcup C^*$
20: **end while**
21: Determine V
22: Solve $\mathrm{BR}\big(W, V, X, L^k, z^k\big)$ to obtain θ^* and $(m_j^*)_{j \in V}$
23: Set $L^{k+1} \leftarrow L^k$, $z^{k+1} \leftarrow z^k + \theta^*$, $(w_j^{k+1} \leftarrow m_j^*)_{j \in V}$, and $u_n^{k+1} \leftarrow u_n^k + \theta^*$
24: Set $k \leftarrow k + 1$
25: Determine Ω^k
26: **if** $\big|\Omega^k\big| < \big|\Omega^{k-1}\big|$ **then** solve Equation (4.6) to obtain p^*
27: Determine $\tilde{\Omega}^k$
28: **until** Ω^k is empty or $\tilde{\Omega}^k$ is empty
29: **return** $\mathbf{w}^k$

(Steps 2-8) The defining WSC instance, WSC(W), is solved to obtain, $X = X(\mathbf{w}^k)$, the set of minimum cost covers at the price point $\mathbf{w}^k = \mathbf{c}$ and $z^k = z(\mathbf{w}^k)$, its attendant overall cost. For deriving all optimal solutions of WSC(W), a binary cut is appended to the original problem to make the previous solution infeasible (i.e., R is updated to contain the previous solution). WSC(W) is then solved again to find another optimum. In the case of a 01 IP, Balas and Jeroslow [2] introduced the well-known binary cut involving no additional variables and one constraint. Within IIA, the minimum weighted set cover C^* denotes the particular solution to WSC(W) and $z^* = \sum_{j \in C^*} (w_j + \tilde{c}_j + \tau)\, x_j$ denotes its associated overall cost. Moreover, solving an infeasible instance of WSC(W) returns solution $C^* = \oslash$ with $z^* = \infty$.

(Step 9) L^k, the set of *bounding covers* is set to C^*, where a bounding cover is a cover whose overall cost is greater than or equal to the cost of the covers in X. (Constraints in subproblem BR ensures this occurs.) In order to fully compute X, it is necessary to determine the first bounding cover.

(Step 10) The set of veto firms (see Definition 2) is determined. A *tight bounding cover* is a cover whose cost is equal to the lowest overall cost of the covers in X. A veto firm is able to unilaterally increase its profits since it can affect an increase in the price of every tight cover in X and L^k by a positive amount, with no tight cover in X or L^k remaining at a lower cost to prevent the profitable price increase. If there is a lowest overall cost cover $C \in X$ or L^k for which a veto firm f does not have a bundle present, then the firms that control the price of C can ensure its price is lower than those covers in which firm f can control the price. This fact prevents a profitable increase in price by f, since the rational customer will always buy the lower cost cover.

(Step 11) The first termination condition is checked. If it is determined that there are no veto firms (i.e., $\Omega^k = \oslash$), then from Proposition 1, a pure strategy Nash equilibrium exists at $\mathbf{w}^k = \mathbf{c}$ and IIA terminates. In this case, the sequence of price points is the singleton $(\mathbf{c})$. If a veto firm exists, IIA continues.

(Step 12) u_f^k, the aggregate unit profit for firm f is set to zero for all $f \in \Omega^k$ and the initial set of active veto firms (see Definition 3), $\tilde{\Omega}^k$, is set to Ω^k.

(Step 13) p^*, the solution to (4.6), indicates the optimal increase in aggregate unit profit for a veto firm in Ω^k. In Γ, the veto firms participate in an embedded Cournot strategic game, in which a veto firm's profit, in the absence of bounding covers, is a function of the total price of the covers in X in which each of the veto firms have bundles. In this sense, the firms engage in a price competition with respect to the pricing of bundles in the same cover, corresponding to a Cournot strategic game. Equation (4.5) describes a veto firm's profit function in this embedded game,

$$P(\mathbf{p}, D, \Omega^k, \Lambda) = p_f \left(d - \eta(\Lambda + p_f + \sum_{i \neq f \in \Omega^k} p_i)^\lambda \right), \tag{4.5}$$

where $\mathbf{p}$ is the vector of the veto firms' aggregate unit profit for the bundles in any cover in X (i.e., $p_f \equiv \sum_{j \in g(f) \bigcap C} (w_j^k - c_j)$ for firm f in a cover C in X), D is the market demand function denoted in (4.1), Ω^k is the set of veto firms at iteration k as defined by Definition 2, and $\Lambda \equiv z^0 + \sum_{h \in \Omega^0 \setminus \Omega^k} (u_h^k)$ is the component of a cover's price that is treated as shared common cost by

the veto firms. The shared common cost of a cover is the sum of the unit costs of all of the bundles in the cover plus the unit profit of the bundles controlled by firms no longer able to increase price as of iteration k (i.e., no longer a veto firm). A Nash equilibrium price point to the Cournot game is labeled as an inter-bundle Cournot equilibrium price point.

Determination of the maximizer of the profit function P provides the aggregate unit profit equilibrium for a veto firm in Ω^k. The first order condition for unit profit maximization is given by

$$\frac{dP}{dp_f}(\mathbf{p}, D, \Omega^k, \Lambda) = d - \eta\lambda p_f(\Lambda + p_f \left|\Omega^k\right|)^{\lambda-1} - \eta\left(\Lambda + p_f \left|\Omega^k\right|\right) = 0. \tag{4.6}$$

Concavity of the market demand function D and the convexity of K_f is sufficient to ensure that the p^* obtained by solving (4.6) is indeed a maximum. Note that $p^* = p_f^*$, for all f in Ω^k due to symmetry. Proposition 2 provides more details concerning the inter-bundle Cournot game.

In steps 14 through 28, the iterative loop executes until one of the two remaining termination conditions is satisfied.

(Step 15) A *pivot firm*, n, is selected from the set of active veto firms, $\tilde{\Omega}^k$. In IIA, the selection rule is to select the lowest indexed firm among the set of firms in $\tilde{\Omega}^k$. The selection rule for determining the pivot firm impacts the sequence of price points generated by IIA.

(Steps 16-20) A while loop executes provided both of the following conditions hold true:

i) for all $C \in L^k$ there exists $j \in g(n) \bigcap C$ such that $w_j^k < \beta_j$,

and,

ii) $z^* < z^k + p^* - u_n^k$.

Condition (i) requires that the pivot firm must have at least one of its bundles present in every cover C in L^k and that the bundle's price not be at its upper bound. Condition (ii) requires that the minimum overall cost associated with the latest solution to WSC(W), z^*, must be less than the minimum overall cost associated with the computed inter-bundle Cournot price point, $z^k + p^* - u_n^k$, a cost which the pivot firm cannot exceed. Within the while loop, WSC(W) is repeatedly solved in order to identify the lowest overall cost bounding cover in which the pivot firm has no bundle. The bounding cover effectively limits the unit profit the pivot firm is able to obtain unilaterally since the pivot firm will not increase the prices of the bundles in the covers in X higher than a bounding cover's overall cost. Similar to steps four through eight, when deriving multiple optimal solutions of WSC(W), a binary cut is appended to each subsequent WSC problem to render previous solutions

infeasible (i.e., R is updated).

(Step 21) The pivot firm's set of veto bundles (see Definition 4) is determined. (Step 22) The best response subproblem, BR, is solved. BR is a piece-wise linear maximization problem, the solution to which provides an optimal weighting for the pivot firm's bundles given constraints regarding the costs of the bounding covers in L^k (found in steps 16 through 20) and maximum bounds on bundle pricing, $(\beta_j)_{j\in V}$. BR is solved for θ^* and $\mathbf{m}^* = (m_j^*)_{j\in V}$, where θ^* denotes the maximum amount of improvement in aggregate unit profit that the pivot firm realizes at the current iteration and m_j^* denotes the optimal weight attributed to veto bundle j in V. Constraint C1 ensures that the maximum aggregate unit profit does not exceed the minimum attainable aggregate unit profit of any single cover in X. Constraint C2 ensures that the overall cost associated with the maximum aggregate unit profit does not exceed the overall cost of any single bounding cover in L^k. Constraint C3 ensures the maximum aggregate unit profit does not result in the inter-bundle Cournot aggregate unit profit margin being exceeded (i.e., it ensures any price decrease is not profitable). Constraints C4 and C5 ensure each veto bundle is priced within acceptable bounds.

$\mathbf{BR}\big(W, V, X, L^k, z^k\big)$

$$
\begin{array}{lrll}
\text{Maximize} & \theta & & \\
\text{subject to} & \theta & \leq \displaystyle\sum_{j\in C\bigcap V} m_j - \sum_{j\in C\bigcap V} c_j, & \text{for all } C\in X, \quad \text{(C1)} \\
& \theta & \leq \displaystyle\sum_{j\in C\bigcap V} m_j + \sum_{j\in B\setminus\{C\bigcap V\}} w_j^k & \\
& & \quad + \displaystyle\sum_{j\in C} (\tilde{c}_j + \tau) - z^k & \text{for all } C\in L^k, \quad \text{(C2)} \\
& \theta & \leq p^* - u_n^k, & \text{(C3)} \\
& m_j & \geq w_j^k & \text{for all } j\in V, \quad \text{(C4)} \\
& m_j & \leq \beta_j & \text{for all } j\in V. \quad \text{(C5)}
\end{array}
$$

(Steps 23-24) L^k, z^k, $\mathbf{w}^k$, u_n^k, and k are updated. (Steps 25-27) The set of veto firms and the set of active veto firms are updated. If the number of veto firms decreases compared to the previous iteration (i.e., the pivot firm did not attain the Cournot profit margin, P), then (4.6) must be solved to compute a new p^* for the new set of veto firms.

(Step 28) The second two termination conditions are checked. If it is determined that there are no remaining active veto firms (i.e., $\tilde{\Omega}^k = \oslash$), then from Proposition 2, a pure strategy Nash equilibrium exists at $\mathbf{w}^k$ with each firm $f \in \Omega^k$ satisfying (4.6). IIA terminates in the following

step. In this case, the sequence of price points is $\left(\mathbf{w}^0, \mathbf{w}^1, \ldots, \mathbf{w}^k\right)$. If an active veto firm exists, IIA continues, returning to step 14.

If there are no remaining veto firms (i.e., $\Omega^k = \oslash$), then from Proposition 3, a pure strategy Nash equilibrium exists at $\mathbf{w}^k$ and IIA terminates in the following step. In this case, the sequence of price points is $\left(\mathbf{w}^0, \mathbf{w}^1, \ldots, \mathbf{w}^k\right)$. If a veto firm exists, IIA continues, returning to step 14.

To determine the complexity of IIA, suppose that the WSC(W) problem instance can be solved in $O(\mathbf{T}_{WSC})$ time. Label M as the maximum number of possible covers that IIA may visit (from Lemma 1, due to Weisstein [60]). Then, given an arbitrary instance of Γ, IIA executes in $O(M \cdot \mathbf{T}_{WSC})$ time to compute a pure strategy Nash equilibrium. IIA's worst-case complexity is due to the repeated calls to solve the WSC problem instances, which in the general case, is *NP*-hard in the strong sense [24] and requires exponential time algorithms for finding exact solutions (unless *P=NP*).

Lemma 1. *The number of possible covers for a set of $|S|$ products is*

$$M \equiv \frac{1}{2} \sum_{i=0}^{|S|} (-1)^i \binom{|S|}{i} 2^{2^{|S|-i}}.$$

4.3 Convergence Theory

This section provides convergence results for IIA by examining the validity of the three termination conditions. A proposition is established for each condition, leading to the main Nash equilibrium existence result for Γ, given by Theorem 1.

Proposition 1 provides necessary and sufficient conditions for the initial price point $\mathbf{w}^0 = \mathbf{c}$ to be a Nash equilibrium. The sequence that terminates immediately is the singleton $(\mathbf{c})$.

Proposition 1 (Termination Condition 1)**.** *Given an instance of Γ and execution of IIA, consider a nonempty collection of lowest overall cost covers, $X = X(\mathbf{c})$, corresponding to a minimum cost $z = z(\mathbf{c})$, where the price point $\mathbf{c} = (c_j)_{j \in B}$ represents the lowest possible price for each bundle in B. The price point $\mathbf{c}$ is a pure strategy Nash equilibrium if and only if Ω^0 is empty.*

Proof. ($\Rightarrow$)
Assume to the contrary that $\mathbf{c}$ is a pure strategy Nash equilibrium and Ω^0 is nonempty. Then, by the definition of Ω^0 (see Definition 2), there exists a firm $f \in N$ that controls at least one bundle

(not at its upper bound in price) in every cover in X. Denote $\delta_j \geq 0$ as the unit increase in price from c_j for bundle $j \in g(f)$. Let $\sum_{j \in g(f) \bigcap C} \delta_j \geq \alpha$ for each cover $C \in X$, where $\alpha > 0$ exists since firm f has at least one bundle (not at its upper bound in price) in C. The unilateral price change by firm f results in a price point $\mathbf{w} \neq \mathbf{c}$, where $w_j = c_j + \delta_j, j \in g(f)$ and $w_j = c_j, j \in g(-f)$. The price change by firm f is profitable since the cost attendant to the inter-bundle Cournot price point is greater than or equal to $z + \alpha$ (i.e., $\frac{dP}{dp_f} > 0$ at $\mathbf{w}$). Firm f's unit profit increases by α, since no cover in X remains at an overall cost less then $z + \alpha$. The profitable price change by firm f contradicts the assumption that $\mathbf{c}$ is a pure strategy Nash equilibrium, and hence, Ω^0 is empty.

($\Leftarrow$) Assume to the contrary that Ω^0 is empty and $\mathbf{c}$ is not a pure strategy Nash equilibrium. Then, by the definition of a Nash equilibrium (see Definition 1), there exists a firm $i \in N$ for which a profitable increase in price exists. Since Ω^0 is empty, there exists a cover $C \in X$ for which firm i cannot increase the price of any of the bundles in C (i.e., no bundle $j \in g(i)$ is a member of the cover C, or if it is a member of C, its price is at its upper bound). If firm i were to increase the aggregate price of bundles belonging to a cover $C' \in X$ by $\alpha > 0$, then the cost of C' would be greater than the lowest overall cost (i.e., $z + \alpha > z$), while the cost of C would remain at z. Therefore, the aggregate price increase of bundles belonging to a cover C' results in zero profit for firm i. Since firm i cannot lower prices from $\mathbf{c}$, it then follows that a profitable change in price for firm i does not exist. This contradicts the non-equilibrium assumption, establishing the Nash equilibrium claim. ■

Proposition 2 provides sufficient conditions for the existence of a pure strategy Nash equilibrium in a Cournot strategic game that directly corresponds to the desired optimal increase in aggregate unit profit for each firm in the set of veto firms. At the inter-bundle Cournot equilibrium price point, the increase or decrease in price of one of the bundles in a cover $C \in X$ (controlled by a veto firm) affects the profit of the other veto firms controlling bundles in C due to the effect of the aggregate price of C on consumer demand. This is precisely the case of the Cournot game, where instead of prices as the strategic variable, quantity produced is considered. By appropriately setting the parameters, the inter-bundle Cournot equilibrium is found by solving the corresponding Cournot game. At iteration k of IIA, while an inter-bundle Cournot equilibrium exists for Ω^k, bounding covers or bundle price bounds reached in later iterations may prevent the attainment of an inter-bundle Cournot equilibrium price point for Ω^k; such an occurrence would require re-computing another equilibrium (i.e., step 26 of IIA) with the new set of veto firms.

Consider a Cournot game in which a single homogeneous product is produced by a set of F firms. The cost to firm $i \in F$ of producing q_i units of the product is $\hat{C}_i(q_i)$, where $\hat{C}_i$ is convex and twice continuously differentiable. Aggregate production is sold at a single market clearing price as determined by an inverse demand function. If the total production in the market is $Q = \sum_{i \in F} q_i$, then the market price is $\hat{P}(Q)$, where $\hat{P}$ is concave and twice continuously differentiable. The assumption of convexity and concavity on the cost and inverse demand functions, respectively, provides sufficient condition for a firm's profit function v_i to be concave in its own output [58], where $v_i = q_i\hat{P}(Q) - \hat{C}_i(q_i)$. Note that the assumption of convexity for cost and of concavity for inverse demand are satisfied by fixed charge cost and linear inverse demand. The following existence result holds.

Lemma 2 (Existence of a Pure Strategy Equilibrium in the Cournot Game)**.** *A pure strategy Nash equilibrium exists at an aggregate output of Q^*, with each firm i producing q_i^*.*

Proof. Determining the Nash equilibrium of such a game is as follows: define the best response production quantity for firm i, $\phi_i(Q)$, by its first order profit maximization condition, $\hat{P}(Q) - \hat{\hat{C}}_i(q_i) + q_i\hat{\hat{P}}(Q) = 0$, where $\phi_i(Q)$ is continuous and nonincreasing due to the assumptions regarding $\hat{C}_i$ and $\hat{P}$. Denote $\Phi(Q) = \sum_{i \in F} \phi_i(Q)$ as the sum of the best response production quantities, where Φ is also continuous and nonincreasing. A pure strategy Nash equilibrium of the Cournot game is found by finding a fixed point of the function $Q \to \Phi(Q)$. Application of a Brouwer's fixed point theorem [4] provides the result. To satisfy the conditions necessary for application of the theorem, the function must be continuous and nonincreasing, and the feasible region compact. $\Phi(Q)$ is continuous and nonincreasing due to the assumptions regarding $\hat{C}_i$ and $\hat{P}$. Compactness is obtained by requiring $0 \leq \Phi(0) < Q$ for all Q such that $\hat{P}(Q) = 0$. Denote the optimal aggregate production as Q^* and the corresponding production of firm i as $q_i^* = \phi_i(Q^*)$. ∎

The results given by Lemma 2 are applied in Proposition 2.

Proposition 2 (Termination Condition 2)**.** *Given an instance of Γ and execution of IIA, if the set of active veto firms, $\tilde{\Omega}^k$, is empty, then a pure strategy inter-bundle Cournot equilibrium exists at $\mathbf{w}^k$.*

Proof. Assume to the contrary that $\tilde{\Omega}^k$, is empty and a pure strategy inter-bundle Cournot equilibrium does not exist at $\mathbf{w}^k$. Execution of IIA results in a sequence of price points, $\mathbf{w}^0, \mathbf{w}^1, \ldots, \mathbf{w}^k$, where the iterative adjustments are made according to the solution to subproblem BR. In BR,

constraints C1 and C2 ensure that at each iteration any change in price results in a price point where the covers in L^k are greater than or equal to the cost of the covers in X. Constraint C3 ensures that at each iteration any change in price results in a price point where $\frac{dP}{dp_f} \geq 0$, which implies that in IIA an aggregate price decrease is always unprofitable. Constraints C4 and C5 ensure that at each iteration any change in price results in a feasible price point.

For the set of firms not in Ω^k, by the definition of Ω^k (see Definition 2), there exists a cover $C \in X$ for which firm $f \notin \Omega^k$ cannot increase the price of any of the bundles in C (i.e., no bundle $j \in g(f)$ is a member of the cover C, or if it is a member of C, its price is at its upper bound). If firm f were to increase the aggregate price of bundles belonging to a cover $E \in X$ by $\alpha > 0$, the cost of E would be greater than the lowest overall cost z^k, while the cost of C would remain z^k. Therefore, any aggregate price increase of bundles belonging to a cover E results in zero profit for firm f. Constraint C3 in subproblem BR of IIA ensures firm f cannot profitably lower prices from $\mathbf{w}^k$. It then follows that a profitable change in price for firm f does not exist.

For the set of firms in Ω^k, the results of a standard Cournot strategic game are applied. At iteration k of IIA, given Ω^k, choose any cover $C \in X$. Let the veto firms in Ω^k equate to the firms in F (i.e., $F \leftarrow \Omega^k$). For each firm $i \in F$, let $q_i \leftarrow \sum_{j \in g(i) \bigcap C} (w_j^k - c_j)$ denote the aggregate unit profit of its bundles in C and let $Q = \sum_{i \in F} q_i$ denote the total aggregate unit profit for all of the firms in Ω^k due to the cover C. Let $\hat{C}_i(q_i) \leftarrow 0$ denote the cost function for firm i. Let $\hat{P}(Q) \leftarrow D(Q + \ell)$ denote the market demand function, where $\ell = \sum_{j \in C} c_j + \tilde{c}_j + \tau + \sum_{f \in \Omega^0 \setminus \Omega^k} u_f^k$ represents the shared constant cost of C for the firms in Ω^k. Recall that the market demand function D satisfies the same properties as the inverse demand function $\hat{P}$. The best response function $\phi_i(Q)$ remains continuous and nonincreasing due to the assumptions on $\hat{C}_i$ and $\hat{P}$. Compactness is satisfied by requiring $\sum_{j \in g(\Omega^k) \bigcap C} (w_j - c_j) > 0$ for any $\mathbf{w}$ such that $D(z(\mathbf{w})) = 0$. The result follows from Lemma 2 where q_i^* denotes the equilibrium aggregate unit profit of firm i for any cover C in X. Since $\tilde{\Omega}^k$ is empty, $u_i^k = \sum_{j \in g(i) \bigcap C} (w_j - c_j) = q_i^*$ for all $i \in \Omega^k$ and $\mathbf{w}^k$ is a price point where a profitable change in price for firm i does not exist.

Since firm $f \notin \Omega^k$ and firm $i \in \Omega^k$ cannot affect a profitable change in price at $\mathbf{w}^k$, no firm in N has the ability to adjust prices to unilaterally increase profit. This contradicts the non-equilibrium assumption, establishing the Nash equilibrium claim. ■

Proposition 3 provides sufficient conditions for the price point $\mathbf{w}^k$ to be a Nash equilibrium. The conditions indicate that if there are no remaining veto firms, then no firm is able to unilaterally

increase profit.

Proposition 3 (Termination Condition 3)**.** *Given an instance of* Γ *and execution of algorithm IIA, if the set of veto firms,* Ω^k*, is empty, then a pure strategy Nash equilibrium exists at* $\mathbf{w}^k$*.*

Proof. Begin with the same initial paragraph given in the proof of Proposition 2.

Since Ω^k is empty, there exists a cover $C \in X$ for which firm $f \in N$ cannot increase the price of any of the bundles in C (i.e., no bundle $j \in g(f)$ is a member of the cover C, or if it is a member of C, its price is at its upper bound). If firm f were able to increase the aggregate price of bundles belonging to a cover $E \in X$ by $\alpha > 0$, the cost of E would be $z^k + \alpha$, greater than the lowest overall cost z^k, while the cost of C would remain at z^k. Therefore, any aggregate price increase of bundles belonging to a cover E results in zero profit for firm f. Constraint C3 in subproblem BR of IIA ensures firm f cannot profitably lower prices from $\mathbf{w}^k$. It then follows that a profitable change in price for firm f does not exist. This contradicts the non-equilibrium assumption, establishing the Nash equilibrium claim. ■

All elements are in place to prove Theorem 1, which guarantees that a pure strategy Nash equilibrium always exists for Γ.

Theorem 1 (Static Game Equilibrium Existence) *Given an instance of* Γ*, a pure strategy Nash Equilibrium always exists.*

Proof. Given an instance of Γ, implement IIA, which provides a sequence of price points $\mathbf{w}^0$, $\mathbf{w}^1$, …, $\mathbf{w}^k$ ending with the price point $\mathbf{w}^k$ satisfying one of three termination conditions. If IIA terminates immediately under Termination Condition 1, Proposition 1 shows $\mathbf{w}^0 = \mathbf{c}$ is a pure strategy Nash equilibrium. If IIA terminates under Termination Condition 2, Proposition 2 shows $\mathbf{w}^k$ is a pure strategy Nash equilibrium (in the limiting sense if L^k is nonempty). If IIA terminates under Termination Condition 3, Proposition 3 shows $\mathbf{w}^k$ is a pure strategy Nash equilibrium (in the limiting sense if L^k is nonempty). The number of iterations in IIA is governed by the maximum number of possible covers. As indicated by Lemma 1, in the worst case, the maximum number of covers, M, is finite. Since there are a finite number of covers IIA must terminate.

IIA provides a sequence of price points $\mathbf{w}^0, \mathbf{w}^1, \ldots, \mathbf{w}^k$ and must terminate with the price point $\mathbf{w}^k$ as a Nash equilibrium. To see this, assume to the contrary that IIA terminates at iteration k, returning $\mathbf{w}^k$. Moreover, assume $\mathbf{w}^k$ is not a Nash equilibrium. For the case when $k = 0$, since $\mathbf{w}^k$

is not a Nash equilibrium, then by the definition of a Nash equilibrium (Definition 1), a profitable change in price exists for some firm i. Since $\mathbf{w}^k = \mathbf{c}$ the profitable change must result from a price increase. Then by the definition of a veto firm (Definition 2), $i \in \Omega^0$ indicating Ω^0 is nonempty, which implies that IIA has not terminated, which is a contradiction. For the case when $k > 0$, since $\mathbf{w}^k$ is not a Nash equilibrium, then by the definition of a Nash equilibrium (Definition 1), a profitable change in price exists for some firm f, implying $u_f^k \neq p^*$. Then by the definition of an active veto firm (Definition 3), $\tilde{\Omega}^k$ is nonempty and since $\tilde{\Omega}^k \subseteq \Omega^k$, then Ω^k is nonempty. $\tilde{\Omega}^k$ and Ω^k nonempty implies that IIA has not terminated, which is a contradiction. These arguments establish that IIA cannot terminate at the price point $\mathbf{w}^k$, where $\mathbf{w}^k$ is not a Nash equilibrium. ■

4.4 The United States Pediatric Vaccine Market

Section 4.4 demonstrates the utility of Γ and Γ^r by applying them to the analysis of the United States public sector pediatric vaccine market. Three different scenarios are examined. The first scenario establishes the economic profit of the vaccine manufacturers based on current vaccine prices. The second scenario applies Γ in order to examine the impact of a Bertrand price competition on the profit levels of the competing vaccine manufacturers. The third scenario applies Γ^r in order to examine the ramifications of tacit collusion on the market. The section begins with a brief description of the market and concludes with a discussion of limitations and general results.

4.4.1 Market Description

The development of pediatric vaccines is a difficult and costly endeavor. In the United States pediatric vaccine market, a relatively small number of pharmaceutical firms engage in the research, development, manufacture, sales, marketing, and distribution of pediatric vaccines [18]. All pediatric vaccines distributed in the United States are manufactured privately, with no obligation to sustain or initiate the production of pediatric vaccines, regardless of the importance of such vaccines to public health. Multiple stakeholders influence the development, licensing, production, and distribution of pediatric vaccines. It behooves these stakeholders to be aware of the complexities of the market in which they participate. The economic competition between pharmaceutical firms and the impact of various public policies on the market warrants detailed analysis.

When investigating the United States pediatric vaccine market, the techniques presented in this

chapter are a natural game theoretic extension to the work of Robbins et al. [51], who provide a methodology for analyzing pricing strategies for competing combination vaccines in the United States pediatric vaccine market, with the goal of maximizing a pharmaceutical company's expected revenue. Since unit production cost was assumed to be negligible, the methodology effectively sought to maximize expected profit. The methodology was applied to a single firm and a single combination vaccine (i.e., a bundle of products) and assumed all other vaccine prices remained constant. The proposed approach represents a single price adjustment in a best response dynamics process. Applied systematically, the competing pharmaceutical companies would continually undercut each other in price in order to achieve higher profits. This market situation is indicative of Bertrand economic competition and clearly lends itself to study via game theory, and more specifically, to study with Γ.

There are numerous stakeholders involved in the United States pediatric vaccine market. The pharmaceutical firms, GlaxoSmithKline, Merck, and Sanofi Pasteur, manufacture the vaccines of interest in this chapter. The Food and Drug Administration (FDA) licenses the use of the vaccines. The Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP), and American Academy of Pediatrics (AAP) recommend proper use of the vaccines. The customers (i.e., state and local government public health officials) purchase vaccines for the immunization of the citizens in their administrative areas of responsibility. Federal government public health officials negotiate the vaccine prices for the purchases made by the state and local governments. Pediatric vaccines purchased at the public sector price, as negotiated by the federal government, account for approximately 57% of total pediatric vaccine purchases by volume [46]. For the results presented in this chapter, only the public sector of the market is considered. However, the methods discussed could also be adapted to the private sector.

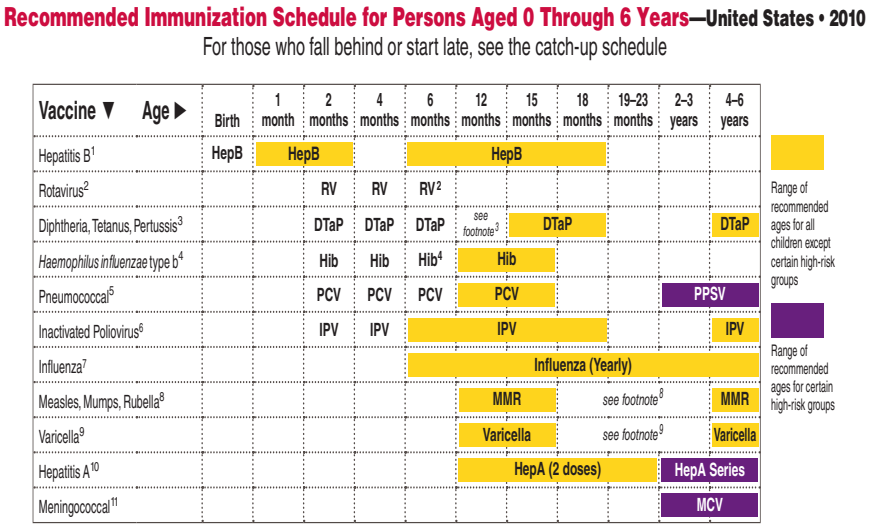
Vaccine development by the pharmaceutical firms requires proficient management of a host of processes, most requiring highly skilled scientists and engineers in order to successfully produce the products [18]. The manufacturing process is expensive and time consuming, requiring vigilant maintenance of stringent FDA regulatory specifications. The estimated total unit production cost of a fully burdened liquid product vaccine (including the costs of filling, vialing, and packaging) is between \$0.70 and \$1.30 [18]. In addition to production costs, there is a federal excise tax associated with each vaccine dose; \$0.75 for each antigen the vaccine contains [13]. Vaccines are slightly differentiated in that they may be packaged in either vials or syringes. This difference

in packaging affects costs with respect to nurse preparation time. Vaccine preparations costs for vials and syringes are assumed to be \$0.75 and \$0.25 per dose, respectively (see [30] or [61] for detailed descriptions). The vaccines of interest in this chapter are those that were licensed in the United States and under federal contract (ending 31 March 2010) for purchase by public-sector immunization programs [5]. Note that monopoly vaccine manufacturers and their products are not included in the analysis. The results presented in this study seek to portray long term market trends; as such, research and development costs are ignored since the actual cost of producing the vaccine with respect to research and development depreciate over time. However, if research and development costs were of direct interest, one could compare the δ-discounted profit stream generated by an alternative investment vehicle for the research and development costs to the δ-discounted profit stream resulting from a likely tacit collusion equilibrium point in the market.

The FDA's licensing and approval process is a requirement for vaccine use in the United States. Following FDA approval, a positive recommendation is very important to the success of a pediatric vaccine. Changes in recommendations or requirements from the CDC, ACIP, or AAP greatly influence the demand for a particular vaccine. These organizations issue numerous guidelines regarding policies to effectively control vaccine-preventable diseases. This includes maintaining a list of acceptable vaccines and publishing an annual schedule concerning the appropriate periodicity and dosages of vaccines, the United States Recommended Childhood Immunization Schedule (RCIS) (see Figure 4.1 from CDC [13]). Public health officials seek to satisfy the RCIS for each child in their administrative area of responsibility in order to ensure proper immunization coverage and promote public health. The five time periods of interest in this study are the following: (1) birth, (2) 2-month, (3) 4-month, (4) 6-month, and (5) 12-18 months.

When formulating Γ instances to model the United States pediatric vaccine market, the RCIS defines the WSC instance that drives customer demand. Indeed, the demand structure reflects a desire by vaccine purchasers to satisfy the RCIS, directly corresponding to finding a minimum cover, where vaccine component antigens cover disease prevention requirements [27]. There is an assumption of rational consumer behavior in that a minimum weighted set cover is sought (i.e., a consumer seeks to satisfy the RCIS at a minimum cost). The analysis presented in this chapter focuses on four *competitive* antigens, which provide protection against the following diseases: diphtheria, tetanus, and pertussis (DTaP), *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), and polio (IPV). These antigens are said to be competitive because more than one firm manufac-

Figure 4.1: United States 2010 Recommended Childhood Immunization Schedule (through Age 6)



tures a vaccine containing the antigen.

Table 4.1 provides a summary of the information describing the United States public sector pediatric vaccine market. This information is used to construct the three scenarios of interest. Column 1 indicates the set of pharmaceutical firms, N (from [5, 20]), column 2 indicates the set of pediatric vaccines, B, where each vaccine contains a subset of the set of antigens, S, sold by the firms (from [13, 20]), column 3 indicates the time periods in the RCIS for which the vaccines are licensed to immunize children (from [5, 20]), and columns 4-8 indicate unit costs per dose. Column 4 indicates the base unit production cost (from [18]), column 5 indicates the federal excise tax associated with each vaccine (from [13]), column 6 indicates the total unit cost for manufacturing the vaccine, $(c_j)_{j \in B}$, column 7 indicates the product differentiation cost vector, $(\tilde{c}_j)_{j \in B}$, and column 8 indicates the maximum allowable price of a vaccine $(\beta_j)_{j \in B}$, (assumed to be the current public sector price, from [5]). In each of the scenarios, there is an assumed cost of \$10.00 associated with each injection (i.e., $\tau = 10$) that the consumer considers. See Glazner et al. [25] for a detailed discussion regarding the costs to healthcare providers for delivering childhood vaccinations.

To characterize the demand function for the Γ instances, three different population and healthcare statistics are required: the number of children completing a RCIS on an annual basis, the vaccine coverage rate among those children completing a RCIS, and the proportion of those children for which the vaccines were purchased at the public sector price. According to a recent National Vital Statistics Report [37], approximately 4.3 million births were registered in the United States in

Table 4.1: Vaccine information

(1) Firm	(2) Vaccine		(3) Available Periods	(4) Prod. Cost	(5) Federal Excise Tax	(6) Total Cost	(7) Diff. Cost	(8) Max Price
GlaxoSmithKline	DTaP	Infanrix®	2, 3, 4, 5	$0.90	$2.25	$3.15	$0.25	$13.75
	Hib	Hiberix®	2, 3, 4, 5	$0.70	$0.75	$1.45	$0.75	$8.66
	HepB	ENGERIX B®	1, 2, 4	$0.70	$0.75	$1.45	$0.25	$9.75
	DTaP-HepB-IPV	Pediarix®	2, 3, 4	$1.30	$3.75	$5.05	$0.25	$48.75
Merck	Hib	PedvaxHIB®	2, 3, 4, 5	$0.70	$0.75	$1.45	$0.75	$11.29
	HepB	RECOMBIVAX HB®	1, 2, 4	$0.70	$0.75	$1.45	$0.75	$10.00
	Hib-HepB	COMVAX®	2, 3, 4	$0.80	$1.50	$2.30	$0.75	$28.80
Sanofi Pasteur	DTaP	Tripedia®	2, 3, 4, 5	$0.90	$2.25	$3.15	$0.75	$13.25
	Hib	ActHIB®	2, 3, 4, 5	$0.70	$0.75	$1.45	$0.75	$8.66
	IPV	IPOL®	2, 3, 4	$0.70	$0.75	$1.45	$0.25	$11.51
	DTaP/Hib	TriHIBit®	5	$1.00	$3.00	$4.00	$0.75	$27.31
	DTaP-IPV/Hib	Pentacel®	2, 3, 4	$1.30	$3.75	$5.05	$0.75	$51.49

2006. These children represent the maximum potential set of consumers of the vaccines. The most recent National Immunization Survey (NIS) results provide estimated vaccine coverage rates for children aged 19-35 months [11]. With respect to the four diseases of interest in this chapter, the NIS provides the proportion of children completing the full schedule (0.782) and the proportion of children completing none of the schedule (0.006). The estimated proportion of children for which full schedules were purchased at public sector prices lies in the interval $(0.782, 0.994)$ and must be estimated using the NIS data.

Denote α as the estimated proportion of the RCIS completed by ρ, the corresponding proportion of children aged 19-35 months. The parameter ρ_1 denotes the coverage rate for the full 4:3:1:3:3 vaccination series (i.e., $\alpha = 1$ for $\rho \in [0, \rho_1]$), which most closely resembles completion of the full RCIS with respect to the four diseases of interest in this chapter. The parameter ρ_2 denotes the proportion of children who received at least one vaccination (i.e., $\alpha = 0$ for $\rho \in [\rho_2, 1]$). The quadratic function $\nu(\rho) = \kappa_1\rho^2 + \kappa_2\rho + \kappa_3$, for $\rho \in [\rho_1, \rho_2]$ represents the coverage rate as a function of the proportion of children. The NIS results do not specify the exact nature of the reduction from full coverage to no coverage. The function $\nu(\rho)$ can be fit to the NIS data and its parameters specified to represent any belief concerning the rate at which coverage decreases. For the results presented in this chapter, a concave relationship is assumed, in which a slow decay of the coverage rate occurs. To compute α set $\rho_1 = 0.782$ and $\rho_2 = 0.994$ (both from [11]) and set $\kappa_1 = -18$; κ_2 and κ_3 are then computed to induce the desired concave curve. Note that $\kappa_1 = -18$ is arbitrary; no empirical data is available to provide a justifiable value. The coverage rate α provides the necessary coverage information for characterizing the Γ demand function, where $\alpha \equiv \rho_1 + \int_{\rho_1}^{\rho_2} \nu(\rho)d\rho = 0.917$.

The market demand function used in the Γ instances reflects the *perfect inelasticity* (see Mankiw [36]) inherent in the United States public sector pediatric vaccine market. The three components discussed above give the following constant demand function: $D\left(z(\mathbf{w})\right)$ where $d = 4,300,000 \cdot 0.917 \cdot$

$0.57 \approx 2,200,000$. Regardless of the price of the vaccines and the overall cost of the minimum cost cover, the demand remains the same. Naturally, this market situation is untenable unless price is bounded in some manner. An exogenous government entity (i.e., Congress) provides funding for the purchase of the vaccines and as one would expect another government entity (i.e., the CDC) effectively caps prices by exercising its monopsonistic leverage with vaccine manufacturers (see Table 4.1, column 8). Moreover, the prices of monovalent vaccines, when purchased using federal funds, are capped by law.

4.4.2 Current Firm Profits

In the first scenario, given the information in Table 4.1, the annual profit of the pharmaceutical firms are determined using the techniques discussed by Robbins et al. [51]. Table 4.2 presents the resulting firm profits. GlaxoSmithKline fares very well due to the slight price advantage of the formulary containing three doses of Pediarix® compared to the formulary containing three doses of Pentacel®. Note that the current price of the pediatric vaccines and the attendant profit levels are not in equilibrium. Indeed, by lowering the price of Pentacel®, Sanofi Pasteur could easily obtain a profit as large as that earned by GlaxoSmithKline. GlaxoSmithKline could then follow suit by again decreasing prices. This repeated undercutting in price leads to an unacceptable result for all of the firms in the market, as shown in the second scenario. Note that the pressure on the price of pediatric vaccines is due in part to the assumption of perfect substitutability among the competing vaccines with respect to satisfaction of the RCIS.

Table 4.2: Firm profits at contract prices ending 31 Mar 2010

Firm	Profit	Cost	Revenue
GlaxoSmithKline	$ 306,680,000.00	$ 36,520,000.00	$ 343,200,000.00
Merck	$ 43,296,000.00	$ 6,380,000.00	$ 49,676,000.00
Sanofi Pasteur	$ 51,282,000.00	$ 8,800,000.00	$ 60,082,000.00

4.4.3 Equilibrium Firm Profits in the Static Game

In the second scenario, three Γ instances are formulated, two for the first and fifth periods of interest and one for the second thru fourth periods of interest. The second thru fourth periods of interest are consolidated into a single weighted set cover in order to address the special attribute of Merck's Hib vaccine; if PedvaxHIB® or Comvax® is administered in the second and third time periods, a Hib dose in the fourth period is not required. Together, the three Γ instances provide insight as

to what would occur should the pharmaceutical companies engage in Bertrand price competition, continually undercutting one another in prices.

IIA finds a pure strategy Nash equilibrium for each of the three Γ instances (see Table 4.3). The vaccine prices computed by IIA for each of the problem instances are *consistent*, in the respect that there are no pricing conflicts. The amalgamation of the Nash equilibria provides a consistent, common pure strategy Nash equilibrium (in the limiting sense) for the entire schedule. GlaxoSmithKline's HepB vaccine increases in price by \$0.50 to match the HepB vaccine offered by Merck. This price change provides an advantage for GlaxoSmithKline in the second thru fourth periods. In the second Γ instance, the formulary (i.e., cover or group of bundles) consisting of three doses of Pediarix® plus two doses of PedvaxHIB® provides the best value to the consumer. The next best lowest cost formulary consists of three doses of Pentacel® and two doses of ENGERIX B®. These two formularies provide the best economic value to a purchaser since they cover the RCIS requirements in five doses. Given the relatively high cost of an injection (with respect to the cost of the vaccines), a rational purchaser greatly values a reduction in the number of injections administered. Another reason these two formularies are so competitive is the Merck Hib advantage. The use of three doses of Pediarix® results in an over-immunization with respect to HepB. However, this loss in value is made up for by Pediarix®'s formulary partner, PedvaxHIB®, whereby a third dose of Hib is unnecessary. With an equivalent number of doses and equal marginal costs, the only difference between the two formularies results from packaging. GlaxoSmithKline packages its vaccine products in prefilled syringes, which takes less nurse preparation time than vaccines packaged in vials, and hence provides a small economic advantage. The GlaxoSmithKline \$0.50 price increase for its HepB vaccine provides a \$1.50 slack in cost that can be exploited. In the last period, Sanofi Pasteur's TriHIBit® provides a one dose savings to its closest competing formulary. Its price is increased to match its competitor. Table 4.3 shows the Nash equilibrium prices.

Table 4.3: Equilibrium prices for the Γ instances

Firm	Vaccine	Current Price [6]	Inst. 1 Nash Equilibrium	Inst. 2 Nash Equilibrium	Inst. 3 Nash Equilibrium	Scenario Nash Equilibrium
GlaxoSmithKline	DTaP	\$13.75	free	free	\$3.15	\$3.15
	Hib	\$8.66	free	\$1.45	\$1.45	\$1.45
	HepB	\$9.75	\$1.95	\$1.95	free	\$1.95
	DTaP-HepB-IPV	\$48.75	free	\$5.55	free	\$5.55
Merck	Hib	\$11.29	free	\$1.45	free	\$1.45
	HepB	\$10.00	\$1.45	\$1.45	free	\$1.45
	Hib-HepB	\$28.80	free	free	free	free
Sanofi Pasteur	DTaP	\$13.25	free	free	free	free
	Hib	\$8.66	free	\$1.45	free	\$1.45
	IPV	\$11.51	free	free	free	free
	DTaP/Hib	\$27.31	free	free	\$14.85	\$14.85
	DTaP-IPV/Hib	\$51.49	free	\$5.05	free	\$5.05

The attendant annual profits and costs attributed to the pharmaceutical firms are indicated for the Nash equilibrium price list (see Table 4.4). In comparing the current market (see Table 4.2) with one that has engaged in a Bertrand price competition, GlaxoSmithKline loses nearly all of its profit, dropping from over $306 million to over $4 million, Merck drops to a zero profit level margin, and Sanofi Pasteur loses the least, down from over $51 million to nearly $25 million.

Table 4.4: Firm profits at static game equilibrium price point

Firm	Profit	Cost	Revenue
GlaxoSmithKline	$ 4,400,000.00	$ 36,520,000.00	$ 40,920,000.00
Merck	$ -	$ 6,380,000.00	$ 6,380,000.00
Sanofi Pasteur	$ 24,970,000.00	$ 8,800,000.00	$ 33,770,000.00

The Nash equilibrium payoffs shown in Table 4.4 indicate that engaging in Bertrand price competition results in a profound loss of profit for all of the pharmaceutical firms competing in the United States public sector pediatric vaccine market. Certainly, pharmaceutical firms are aware that systematic reductions in price negatively impacts future profits, especially considering the price inelasticity in this market. The current vaccine prices and their corresponding adjustments in recent years reflect this understanding. Moreover, the Γ results are economically naive, as discussed in Section 2.2. Recall that Γ is a static game with no mechanism to model ongoing or repeated interaction between the competing firms. As such, there is no incentive for firms to cooperate in any manner. Collusion in any form is not allowed. Therefore, Γ^r enables a more realistic analysis.

4.4.4 Equilibrium Firm Profits in the Repeated Game

In the third scenario, three Γ^r instances models the pediatric vaccine market, where a pharmaceutical firm must consider the effect of its current pricing strategy on the pricing strategies of other firms in the future and the attendant impact on its own future profits. The Nash equilibrium of vaccine prices determined for each of the Γ^r instances are consistent, in that there are no pricing conflicts. The amalgamation of the three equilibria provides a single, consistent equilibrium. Assume that current prices reflect a price limit, indicating firms can only decrease prices in order to reach an amicable arrangement.

The focal equilibrium price point is selected based on the current component prices within the two most competitive formularies (i.e., the Pediarix® dominant formulary and the Pentacel® dominant formulary; see Table 4.5) and the assumption that Sanofi Pasteur and Merck would reduce the price of the vaccines in the more expensive of the two formularies, the Pentacel dominant formulary, so

Table 4.5: Focal equilibrium vaccine formularies

Firm	Vaccine	Pediarix® Dominant Formulary	Pentacel® Dominant Formulary
GlaxoSmithKline	HepB	1	0
	DTaP-HepB-IPV	3	0
Merck	Hib	2	0
	HepB	0	3
Sanofi Pasteur	DTaP/Hib	1	1
	DTaP-IPV/Hib	0	3

that the two dominant formularies are equal in cost from a vaccine purchaser's perspective. The equilibrium result holds assuming each pharmaceutical firm values future profits sufficiently high.

Table 4.6 shows the Nash equilibrium prices for Γ^r. In order to obtain the Nash equilibrium prices for the repeated game, Merck reduces the price of its HepB from \$10.00 per dose to \$9.25 per dose and Sanofi Pasteur reduces the price of Pentacel® from \$51.49 per dose to \$49.61 per dose. The attendant market shares of these two formularies are evenly split, where the firms produce pediatric vaccines so that 1.1 million schedules are satisfied using the Pediarix® dominant formulary and 1.1 million schedules are satisfied using the Pentacel® dominant formulary.

Table 4.6: Equilibrium prices for Γ^r

Firm	Vaccine	Current Price [6]	Nash Equilibrium
GlaxoSmithKline	DTaP	\$13.75	\$13.75
	Hib	\$8.66	\$8.66
	HepB	\$9.75	\$9.75
	DTaP-HepB-IPV	\$48.75	\$48.75
Merck	Hib	\$11.29	\$11.29
	HepB	\$10.00	\$9.25
	Hib-HepB	\$28.80	\$28.80
Sanofi Pasteur	DTaP	\$13.25	\$13.25
	Hib	\$8.66	\$8.66
	IPV	\$11.51	\$11.51
	DTaP/Hib	\$27.31	\$27.31
	DTaP-IPV/Hib	\$51.49	\$49.61

The Nash equilibrium payoffs shown in Table 4.7 indicate that in the long run, the firms benefit greatly from maintaining the pediatric vaccines at the focal equilibrium price point indicated in Table 4.6. In comparing the market where the firms tacitly collude with one that has engaged in Bertrand price competition, on an annual basis GlaxoSmithKline earns nearly \$149 million more, Merck earns over \$47 million more, and Sanofi Pasteur earns over \$173 million more. Assuming that the firms continue to tacitly collude by employing grim trigger strategies and that each firm's condition on its discount factor is met (see rightmost column in Table 4.7), these higher profit levels can be sustained. If any firm breaks the arrangement, Bertrand behavior results, ultimately leading to the Nash equilibrium outcome shown in Table 4.4.

Note that should a desire for a different profit allocation amongst the firms motivate a requirement for a new focal equilibrium point, an alternative means for attaining the new allocation could be

Table 4.7: Firm profits at repeated game equilibrium price point 1

Firm	Profit	Cost	Revenue	$\delta_f \geq$
GlaxoSmithKline	$ 153,340,000.00	$ 18,260,000.00	$ 171,600,000.00	0.507
Merck	$ 47,388,000.00	$ 7,986,000.00	$ 55,374,000.00	0.079
Sanofi Pasteur	$ 198,330,000.00	$ 25,476,000.00	$ 223,806,000.00	0.459

reached by stipulating production limits as part of the collusive agreement. The equilibrium price point would not change; instead, production levels for the pertinent vaccines would adjust to reflect a self-imposed capacity constraint. For example, if GlaxoSmithKline desires profits approximately equal to those earned by Sanofi Pasteur, yet still desires the price point indicated in Table 4.6, then it becomes a matter of producing the appropriate quantity in order to meet the required profit target levels. Agreeing to limit production to induce market shares of 57.5% and 42.5% for the Pediarix® dominant formulary and Pentacel® dominant formulary, respectively, results in the profit levels seen in Table 4.8.

Table 4.8: Firm profits at repeated game equilibrium price point 2

Firm	Profit	Cost	Revenue	$\delta_f \geq$
GlaxoSmithKline	$ 176,308,000.00	$ 20,988,000.00	$ 197,296,000.00	0.431
Merck	$ 46,772,000.00	$ 7,744,000.00	$ 54,516,000.00	0.091
Sanofi Pasteur	$ 176,308,000.00	$ 22,968,000.00	$ 199,276,000.00	0.528

4.4.5 Discussion

One should note that there are several factors that are not included in this analysis, including important economic factors that could impact the payoffs of the firms in the market of interest. The exclusion of such factors is due to the lack of data or economic models regarding them. These include factors that further differentiate between manufacturer products (e.g., safety and efficacy), as well as costs associated with reduced cold storage handling that result from reductions in the number of separate vaccines necessary to satisfy the RCIS. Other factors not included are brand loyalty, volume discounting, and formulary inertia, due to the difficulty in quantifying economic model parameters describing them. Moreover, treatment of catch-up and high-risk immunization groups is not considered and could certainly impact the desirability of vaccines (e.g., monovalent vaccines may be more desirable in catch-up situations). The risk of vaccine shortages may also impact the analysis, but is not explicitly included in the study. For example, the formulary for the 2-month time period, consisting of one dose of Pediarix and one dose of PedvaxHIB®, is very cost effective; however, if the risk of shortage for Merck's PedvaxHIB® was considered too high (or

indeed, if PedvaxHIB® was currently unavailable), then a risk adverse vaccine purchaser may select the next best formulary despite its additional cost, so as to avoid the possibility of not satisfying the RCIS. Such concerns regarding the risk of shortage is not explicitly modeled in Γ, although by modifying the set of available vaccines, such concerns could be examined.

Higher prices, while seemingly disadvantageous to the purchaser, may be warranted in the bigger picture. Indeed, issues exogenous to the model may be of concern. For example, in the United States public sector pediatric vaccine market, it is in the best interest of the government to pay higher prices in order to prevent vaccine manufacturers from exiting the market [45, 50]. This rationale is motivated primarily by concerns regarding the stable supply of vaccines; when a vaccine is produced by a small number of manufacturers, production problems create immediate, acute shortages. Providing financial incentives, in the form of higher profit margins, encourages firms to enter and remain in the pediatric vaccine market. A robust number of firms in the market benefits society by securing the vaccine supply and enabling the development of future vaccines.

4.5 Conclusions

Γ is a generalization of Bertrand price competition that provides a mathematical framework for the analysis of markets in which a consumer makes purchasing decisions based on the outcome of an associated WSC problem. The Nash equilibrium solution concept provides a consistent mechanism by which rational and intelligent pricing behavior of the firms in Γ can be examined. Theorem 1 indicates a pure strategy Nash equilibrium of the static game Γ always exists. The algorithm introduced enables computation of a Nash equilibrium and also provides the means for constructing the theory for the existence of an equilibrium. Development of Γ^r addresses the often problematic temporal assumption of a single economic interaction between firms. Indeed, firms are likely to interact repeatedly in the market of interest; the repeated game structure enables examination of more realistic market equilibria. Theorem 2 provides conditions by which a subgame-perfect Nash equilibrium of the repeated game Γ^r exists.

The proposed static game provides an appropriate mathematical framework by which to analyze oligopolistic interactions in markets such as the United States public sector pediatric vaccine market. A meaningful understanding of important issues affecting the market of interest is gained. Stakeholders more thoroughly comprehend the consequences of their own actions as well the actions of other stakeholders. Moreover, the holistic impact of rational and intelligent individual

stakeholder on the market provides valuable insight. Such information can be leveraged to improve a single stakeholder's position or influence policy decisions that affect the market in its entirety for the betterment of all parties involved.

CHAPTER 5

THE ALTRUISTIC MONOPSONIST VACCINE FORMULARY PRICING AND PURCHASING PROBLEM: INFORMING PUBLIC HEALTH POLICY

Vaccination is one of the most important and successful public health endeavors in human history, profoundly reducing the number of mortalities caused by infectious diseases [46, 49]. In the United States, the incidence of many childhood diseases has dramatically decreased, even as the number of vaccine-preventable diseases has increased [46]. Yet, by some measures the pediatric vaccine industry is quite fragile [46]. To ensure the safe, secure, and reliable provision of vaccines, the economic interests of the vaccine industry must be considered by public health policy makers.

The United States pediatric vaccine industry consists of a relatively small number of pharmaceutical companies engaged in the research, development, manufacture, and distribution of pediatric vaccines. Participation in the vaccine industry is a difficult, costly, risky, and most importantly, *voluntary* enterprise. All pediatric vaccines distributed in the United States are manufactured by privately held companies, with no obligation to sustain or initiate the production of pediatric vaccines, regardless of the importance of such vaccines to public health [18, 62]. Over the past forty years, the manufacture of pediatric vaccines has become less profitable due to rising costs and limited demand, inducing many pharmaceutical companies to exit the market [18, 45]. As of 2010, just six pharmaceutical companies manufacture vaccines for young children, three of which manufacture only one pediatric vaccine [6]. The contraction of the pediatric vaccine market negatively impacts the provision of vaccines. When a vaccine is produced by a small number of manufacturers, production problems create immediate, acute shortages. In order to ensure adequate immunization coverage levels, a robust vaccine industry is vital to the nation's public health and well being.

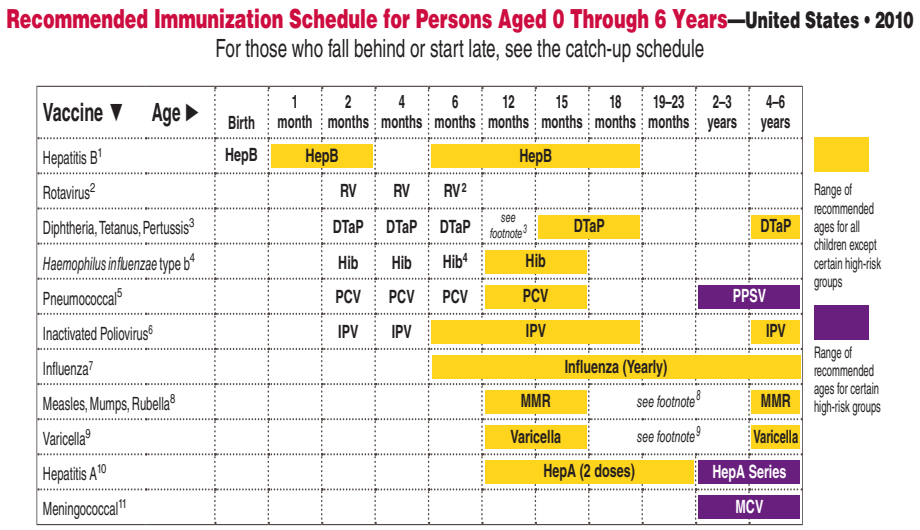
A substantial number of public health policy experts have highlighted factors that would assist in sustaining the current supply of vaccines, as well as encourage the development of new vaccines [18, 28, 38, 45, 46, 50]. Typically, recommendations concerning the vaccine industry's robustness involve financial incentives. For example, Hinman [28] suggests pricing a vaccine in advance based on its estimated social value. McGuire [38] offers an economic model to facilitate the determination

of such prices, reporting that while vaccines have high social value (see Zhou et al. [62] for a full analysis concerning the economic benefit of vaccines to society), the vaccine manufacturers do not receive appropriate financial incentives for participation in the market. Many public health experts contend that vaccine manufacturers should earn higher returns on their investments in order to sustain and expand the production of vaccines [18, 28, 38, 45, 46, 50].

The monopsonistic market power of the federal government uniquely positions it to significantly influence the pediatric vaccine market by negotiating contractual agreements that increase the vaccine manufacturers' financial incentives to remain in the market. Pediatric vaccines purchased at the public sector price, as negotiated by federal government officials at the Centers for Disease Control and Prevention (CDC), account for approximately 57% of total pediatric vaccine purchases by volume [28, 46]. In the United States, the CDC acts as the primary federal public health organization responsible for setting pediatric immunization policy. Based on recommendations from the Advisory Committee on Immunization Practices (ACIP), the CDC annually publishes a Recommended Childhood Immunization Schedule (RCIS) (see Figure 5.1 from [13]) that provides specific guidance regarding the effective control of vaccine-preventable diseases, to include the appropriate periodicity and dosage requirements for each pediatric vaccine. The RCIS serves as the fundamental force driving market demand; vaccine purchasers buy vaccines in order to fully immunize children in accordance with the RCIS. The CDC also maintains a list of acceptable pediatric vaccines (i.e., licensed by the Food and Drug Administration (FDA) [21]) and negotiates discounted prices at which federal, state, and local governments can purchase the vaccines. A model that addresses the short term need to satisfy the RCIS at minimum economic cost while accounting for long term concerns regarding the vaccine industry's viability provides value to the public health community (specifically, the CDC) and is the focus of this research.

Operations research methods have been applied to the analysis of the United States pediatric vaccine market. Prior research was reviewed in Section 2.1. This research effort addresses the issue of the pediatric vaccine industry's continuing viability from the perspective of the monopsonistic federal government. The fundamental premise of the analysis is the supposition that the altruistic CDC desires to negotiate pediatric vaccine prices and determine purchase quantities in order to minimize the vaccine system's delivery costs while ensuring that the pharmaceutical companies manufacturing the pediatric vaccines each earn a profit that induces them to remain in the market. The operations research approach presented in this chapter defines the Altruistic Monopsonist

Figure 5.1: United States 2010 Recommended Childhood Immunization Schedule (through Age 6)



Vaccine Formulary Pricing and Purchasing Problem (AMVF3P) mixed integer non-linear program (MINLP) model, which minimizes the weighted sum of the cost to fully immunize a birth cohort according to a given childhood immunization schedule. The model determines optimal vaccine prices and purchase quantities while ensuring that each vaccine manufacturer earns at least a particular amount of profit, with vaccine production quotas, capacities, and price caps respected. The AMVF3P MINLP model can be used to design a pricing and purchasing policy for the CDC that establishes a sustainable and stable capital investment environment in which the reliable provision of the pediatric vaccines (so essential to public health) can occur.

The chapter is organized as follows. Section 5.1 presents the MINLP model formulation for the optimization problem AMVF3P that determines the set of pediatric vaccine formularies and attendant component vaccine prices and quantities that should be used to satisfy a given childhood immunization schedule for an entire birth cohort. The model minimizes overall system cost while ensuring a sustainable market environment for vaccine manufacturers. Section 5.2 presents the computational complexity of AMVF3P. Section 5.3 reports the computational results of applying the AMVF3P MINLP model to the analysis of CDC pricing and purchasing policies; optimal pediatric vaccine prices and purchase quantities for the current United States pediatric vaccine market are reported. Section 5.4 provides concluding comments and directions for future research.

5.1 Model Formulation

This section presents the MINLP model formulation for AMVF3P, which is used to determine a set of vaccine formularies, the quantity of each vaccine formulary to be purchased, and the prices of the vaccines within the vaccine formularies for a given market environment. The prices and quantities of the vaccines must be chosen so as to minimize the weighted sum of the cost to fully immunize a given birth cohort, while ensuring the vaccine manufacturers each earn at least a specified amount of profit. Moreover, minimum production quotas, maximum capacity limitations, and price caps for each of the vaccines must be respected. Several sets and parameter definitions are required to precisely describe the pediatric vaccine market. Let

$T = \{1, 2, \ldots, \tau\}$: set of time periods for a given childhood immunization schedule.

$D = \{1, 2, \ldots, \delta\}$: set of diseases requiring immunization.

$V = \{1, 2, \ldots, \upsilon\}$: the set of vaccines available to immunize against the diseases in D.

$M = \{1, 2, \ldots, \mu\}$: set of pharmaceutical companies manufacturing the vaccines in V.

$F = \{1, 2, \ldots, \phi\}$: set of vaccine formularies.

$n_d \in \mathbb{Z}^+$: number of vaccine doses that must be administered for immunization against disease $d \in D$ in a single schedule.

$r_v \in \mathbb{Z}^+$: minimum total number of doses of vaccine $v \in V$ that must be purchased.

$k_v \in \mathbb{Z}^+$: maximum total number of doses of vaccine $v \in V$ that can be produced.

$L_v \in \Re^+$: maximum price (weight) allowable for vaccine $v \in V$.

$C_v \in \Re^+$: cost incurred to produce vaccine $v \in V$.

$\tilde{C}_v \in \Re^+$: ancillary cost to immunize patient using vaccine $v \in V$ (i.e., nurse preparation cost and cost of injection).

$P_m \in \Re^+$: total profit each manufacturer $m \in M$ must earn (as negotiated by CDC and industry representatives).

$N \in \Re^+$: number of children that must complete a schedule (i.e., size of the birth cohort).

$I_{vd} = 1$ if vaccine $v \in V$ immunizes against disease $d \in D$, 0 otherwise (i.e., a set of binary parameters that indicate which vaccines immunize against which diseases).

$S_{djt} = 1$ if in time period $t \in T$, a vaccine may be administered to satisfy the jth dose requirement for disease $d \in D$, $j = 1, 2, \ldots, n_d$, 0 otherwise (i.e., a set of binary parameters that indicate the set of time periods during which a particular vaccine dose could be administered to immunize against a disease).

$G_{vm} = 1$ if vaccine $v \in V$ is produced by manufacturer $m \in M$, 0 otherwise (i.e., a set of binary parameters that indicate which manufacturer produces which vaccines).

These sets and parameters provide a robust framework for describing an arbitrary pediatric vaccine market. Note that the problem formulation is due in part from Hall et al. [27] in analyzing pediatric vaccine formulary selection problems; their extensive analysis of childhood immunization schedules is applicable to AMVF3P due to the supposition that health care policy makers attempt to fully immunize children according to a particular childhood immunization schedule. Using the terminology introduced by Hall et al. [27], satisfaction of the 2010 RCIS can be identified as a GVFSP-MED problem instance, in which every disease has mutually exclusive doses with respect to periodicity.

The following decision variables capture the pricing and purchasing policy decisions in AMVF3P. Let

$W_v \in \Re^+$: negotiated price (weight) of vaccine $v \in V$.

$Y_f \in \Re^+$: number of children immunized using vaccine formulary $f \in F$.

$X_{ftv} = 1$ if vaccine $v \in V$, in formulary $f \in F$, is administered in time period $t \in T$, 0 otherwise.

AMVF3P is formulated as a MINLP, a mathematical program with continuous and discrete decision variables and a nonlinear objective function and (or) constraints. The MINLP lends itself well to the formulation of problems where the system structure and parameters must be simultaneously optimized. In AMVF3P, the system structure is the set of vaccine formularies; the parameters are the number of children vaccinated using a particular formulary and the prices of the vaccines in the formularies. MINLPs have been applied to a wide variety of different fields, including finance, engineering, management science, and operations research [57]. Specific problems addressed include portfolio selection, chemical engineering batch processing, design of transmission networks, and automobile manufacturing processes [57]. The MINLP formulation described in this chapter addresses optimal policy decision-making within the field of health care management science. The formal presentation of the AMVF3P MINLP model follows:

AMVF3P

Minimize $\sum_{f\in F}\sum_{t\in T}\sum_{v\in V} Y_f\left(W_v+\tilde{C}_v\right)X_{ftv}$ (O)

subject to

$\sum_{t\in T}\sum_{v\in V} S_{djt}X_{ftv}I_{vd}\geq 1$ for all $f\in F$, $d\in D$, $j=1,2,\ldots,n_d$, (1)

$X_{ftv}\in\{0,1\}$ for all $f\in F$, $t\in T$, $v\in V$, (2)

$\sum_{f\in F}\sum_{t\in T}\sum_{v\in V} Y_f\left(W_v-C_v\right)G_{vm}X_{ftv}\geq P_m$ for all $m\in M$, (3)

$\sum_{f\in F} Y_f = N$ (4)

$r_v\leq\sum_{f\in F}\sum_{t\in T} Y_f X_{ftv}\leq k_v$ for all $v\in V$, (5)

$C_v\leq W_v\leq L_v$ for all $v\in V$. (6)

The objective function (O) minimizes the weighted sum of the cost to immunize a birth cohort of N children subject to the six sets of constraints. Constraint (1) ensures that for each vaccine formulary $f\in F$, at least one vaccine that immunizes against disease $d\in D$ is administered in some time period when dose $j=1,2,\ldots,n_d$ can be administered. Constraint (2) enforces the binary nature of the decision to use or not use a vaccine $v\in V$ in period $t\in T$ in formulary $f\in F$. Constraint (3) ensures that each vaccine manufacturer $m\in M$ makes a profit at least as much as its target profit level, P_m. Constraint (4) ensures that all children satisfy the given childhood immunization schedule. Constraint (5) ensures that each vaccine $v\in V$ meets the required minimum purchase and maximum production levels. Constraint (6) ensures that the price of each vaccine $v\in V$ does not fall below its unit cost nor exceed its price cap.

5.2 Computational Complexity

This section presents the computational complexity of AMVF3P. In the worst case, the problem is shown to be intractable.

Theorem 4. *AMVF3P is NP-hard.*

Proof. Let U, $B=\{B_1,B_2,\ldots,B_n\}$, and $(w_j)_{j\in B}$ denote an arbitrary instance of the weighted set covering optimization problem (WSC): Given U, a set of elements, and B, a set of weighted subsets of U, find a collection Z of subsets from B such that Z covers all elements in U at an overall minimum cost. Define the corresponding particular instance of AMVF3P as follows: Set $D=U$, $V=B$, $(C_v)_{v\in V}=(w_j)_{j\in B}$, $N=1$, $T=\{1\}$, $M=\{1\}$, $F=\{1\}$, $n_d=1$ for all $d\in D$, $S_{djt}=1$, $d\in D$, $j=1$ and $t=1$ for all $d\in D$, $L_v=C_v$ for all $v\in V$, $\tilde{C}_v=0$ for all $v\in V$, $G_{vm}=1$,

$v \in V$, $m = 1$, $P_m = 0$, and $r_v = 0$, $k_v = 1$ for all $v \in V$. Suppose that there exists a polynomial time algorithm to determine X_{ftv} for AMVF3P. Then, by design, the arbitrary instance of WSC can be solved in polynomial time. In particular, given the polynomial time Turing reduction from WSC to AMVF3P, $(Z_j)_{j \in B} = (X_{ftv})_{v \in V}$ solves the arbitrary instance of WSC defined by U, B, and $(w_j)_{j \in B}$. Therefore, since WSC is *NP*-hard (see Garey and Johnson [24]), then AMVF3P is *NP*-hard. ■

Although AMVF3P is *NP*-hard, software exists that provides solutions for small instances of the problem. The AMVF3P instances that represent the current United States pediatric vaccine market are sufficiently small that exact results can be obtained in a reasonable amount of time.

5.3 Results and Analysis

This section reports computational results demonstrating the practical value of the AMVF3P MINLP model. Two different CDC vaccine procurement policies in the public sector of the United States pediatric vaccine market are analyzed. In Scenario 1, no constraint is placed on the minimum number of doses that must be purchased nor on the maximum number of doses that can be produced. The maximum number of formularies allowed in this policy scenario is two. In Scenario 2, it is assumed policymakers wish to purchase at least $500,000$ doses of each vaccine. The maximum number of formularies allowed in this policy scenario is four. Comparisons between the two policies provide insight into the tradeoffs between minimizing costs and increasing the robustness of vaccine supply. The section begins with a brief description of the market. Sections 5.3.1 and 5.3.2 present the results for Scenarios 1 and 2, respectively. Section 5.3.3 presents a discussion of the general results.

Vaccine research and development requires proficient management of a host of processes, most requiring highly skilled scientists and engineers in order to successfully produce the products [18]. The manufacturing process is expensive and time consuming, requiring vigilant maintenance of stringent FDA regulatory specifications. The estimated total unit production cost of a fully burdened liquid product vaccine (including the costs of filling, vialing, and packaging) is between \$0.70 and \$1.30 [18]. In addition to production costs, there is a federal excise tax associated with each vaccine dose; \$0.75 for each antigen the vaccine contains [13]. Vaccines are slightly differentiated in that they may be packaged in either vials or syringes. This difference in packaging affects costs with

respect to nurse preparation time. Vaccine preparations costs for vials and syringes are assumed to be \$0.75 and \$0.25 per dose, respectively (see [30] or [61] for detailed descriptions).

Table 5.1: Rule for vaccine unit production cost determination

No. Antigens	Unit Cost
1	\$0.70
2	\$1.00
3	\$1.30
4	\$1.60
5	\$1.90

Further explanation regarding the vaccine unit production costs used in this chapter is warranted. Douglas et al. [18] report that the fully burdened unit production cost for bulk vaccines manufactured in the United States is approximately \$0.70 to \$1.30. This range represents the authors' viewpoint due to their collective industry experience (as of 2005). However, it is unclear if they accounted for the production of the more complex combination vaccines which have recently come into the market. Therefore, for the results presented in this chapter, the base unit production cost for each vaccine is calculated according to the rule shown in Table 5.1, based in part upon the information provided by Douglas et al. [18], where the unit production cost of the vaccine is a function of the number of antigens it contains.

The vaccines of interest in this chapter are those that were licensed in the United States and under federal contract (ending 31 March 2011) for purchase by public-sector immunization programs [13, 6]. Note that monopoly vaccine manufacturers and their products are not included in the analysis. The single product available would be trivially selected and its price calculated so as to meet the required manufacturer profit level; no meaningful analysis is accomplished. Merck's measles, mumps, and rubella (MMR) combination vaccine and Wyeth's Pneumococcal 13-valent (PCV) vaccine are examples of monopoly products excluded from this analysis.

The AMVF3P MINLP model enforces the structure and rules of pediatric immunization (periodicity and dosage constraints) as recommended by the ACIP [9, 13]. The six time periods of interest in this study include: (1) birth-month, (2) month 2, (3) month 4, (4) month 6, (5) month 12-18, and (6) year 4-6 periods. The analysis presented in this chapter focuses on four *competitive* immunogenic antigens, administered to induce acquired immunity in a patient against the following diseases: diphtheria, tetanus, and pertussis (DTaP), *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), and polio (IPV). These antigens are said to be competitive because more than one pharmaceutical company manufactures a vaccine containing the antigen. A vaccine can only be administered for diseases and in time periods for which it has been licensed by the FDA [21]. It is

assumed that a monovalent HepB vaccine birth dose is administered to all newborns in the birth cohort prior to discharge from the hospital.

Table 5.2: Vaccine information

(1) Manufacturer	(2) Vaccine		(3) Available Periods	(4) Prod. Cost	(5) Federal Ex. Tax	(6) Total Cost	(7) Prep. Cost	(8) Max Price
GlaxoSmithKline	DTaP	Infanrix®	2, 3, 4, 5, 6	$1.30	$2.25	$3.55	$0.25	$14.25
	Hib	Hiberix®	5	$0.70	$0.75	$1.45	$0.75	$8.66
	HepB	ENGERIX B®	1, 2, 4	$0.70	$0.75	$1.45	$0.25	$10.25
	DTaP-IPV	Kinrix®	6	$1.60	$3.00	$4.60	$0.25	$48.00
	DTaP-HepB-IPV	Pediarix®	2, 3, 4	$1.90	$3.75	$5.65	$0.25	$70.72
Merck	Hib	PedvaxHIB®	2, 3, 4, 5	$0.70	$0.75	$1.45	$0.75	$22.77
	HepB	RECOMBIVAX HB®	1, 2, 4	$0.70	$0.75	$1.45	$0.75	$10.25
	Hib-HepB	COMVAX®	2, 3, 4	$1.00	$1.50	$2.50	$0.75	$43.56
Sanofi Pasteur	DTaP	Tripedia®	2, 3, 4, 5, 6	$1.30	$2.25	$3.55	$0.75	$14.25
	Hib	ActHIB®	2, 3, 4, 5	$0.70	$0.75	$1.45	$0.75	$8.83
	IPV	IPOL®	2, 3, 4, 6	$0.70	$0.75	$1.45	$0.25	$11.74
	DTaP-Hib	TriHIBit®	5	$1.60	$3.00	$4.60	$0.75	$46.346
	DTaP-IP-HI	Pentacel®	2, 3, 4	$1.90	$3.75	$5.65	$0.75	$75.33

Table 5.2 provides a summary of the information describing the public sector of the United States pediatric vaccine market. This information is used when constructing AMVF3P instances for the policy scenarios of interest. Column 1 indicates the vaccine manufacturers (from [6, 21]), column 2 indicates the pediatric vaccines, (from [6, 21]), column 3 indicates the time periods in the RCIS for which the vaccines are licensed by the FDA to immunize children (from [13, 21]), and columns 4-8 indicate unit costs per dose. Column 4 indicates the base unit production cost (based on [18]), column 5 indicates the federal excise tax associated with each vaccine (from [6]), column 6 indicates the total unit cost for manufacturing the vaccine, column 7 indicates the product differentiation cost vector (see [30] or [61]), and column 8 indicates the maximum allowable price of a vaccine (assumed to be the current public sector price for monovalents and the current private sector price for polyvalents (from [6]). There is an assumed cost of $10.00 associated with each injection that the consumer considers when making a purchasing decision. The cost of an injection reflects the value the purchaser places on reducing the number injections required to satisfy the RCIS. This reduction in the number of injections is accomplished through the use of combination vaccines, which immunize against multiple diseases in a single injection. See Glazner et al. [25] for a detailed discussion regarding the costs to health care providers for delivering childhood vaccinations.

According to a recent National Vital Statistics Report [37], 4.3 million births were registered in the United States in 2006. These children represent the maximum potential set of consumers of the vaccines. However, pediatric vaccines purchased at the public sector price, as negotiated by federal government officials at the CDC, account for only approximately 57% of total pediatric vaccine purchases by volume [28, 46], reducing the size of the birth cohort for which the CDC should plan.

Moreover, accurate vaccine coverage rates for children (aged 0-6 years) completing the full RCIS using pediatric vaccines purchased at the public sector price are not available (but are certainly less than 100%). For the most pertinent information, see the most recent National Immunization Survey (NIS) for estimated vaccine coverage rates for children aged 19-35 months [11]. It is difficult to specify the exact number of children for which CDC officials should plan; CDC officials would determine such a number based on budgetary and other considerations. For the analysis presented in this chapter it is assumed that for planning purposes at the CDC, the size of the birth cohort is 2.3 million children; moreover, it is assumed these children satisfy the RCIS using pediatric vaccine formularies recommended by the CDC and the vaccines are purchased at contract prices negotiated by the CDC.

To proceed with the development of a realistic policy, it remains to specify appropriate profit levels for the three vaccine manufacturers of interest. It is beyond the scope of this chapter to advise a legitimate target profit value for each manufacturer; such a determination should occur directly (and indirectly) in discussions between CDC officials and industry representatives when establishing federal contract prices for the vaccines. Therefore, although total industry profit and a rule for the apportionment of that profit are provided here, real-world values will be negotiated as described above, with health care policy-makers assessing and scrutinizing the target profit levels used. One should note the difficult and sensitive nature of having government officials specify profits for individual pharmaceutical companies. The delicate matter of specifying profit levels could be viewed as an allocation of industry profit, with actual dollar amounts resulting from an open collaboration of public health care policy experts from government, the medical community, and the vaccine industry. This issue brings to light the delicate balance between allowing markets to determine vaccine prices and capacity, and the need to provide vaccines to enhance public health. Clearly, no easy answers exist for resolving such a complex problem.

An approximate value for the total industry profit earned (as a result of vaccine sales for those containing the four competitive antigens under consideration) can be computed from the results provided by Robbins et al. [51]. Given the current RCIS and current pediatric vaccine prices, there is an estimated total industry profit of approximately $400 million annually. Note that this value does not take into account research and development costs borne by the industry.

A rule for the apportionment of the total industry profit enables specification of the profit levels each manufacturer should earn. The rule is based upon a manufacturer's participation in the

Table 5.3: Total production cost to complete 2010 RCIS by monovalent vaccine

Vaccine	Doses	Cost / Dose	Subtotal
HepB	3	$1.45	$4.35
DTaP	5	$3.55	$17.75
Hib	4	$1.45	$5.80
IPV	4	$1.45	$5.80

Table 5.4: Rule for apportionment of total industry profit

	Vaccine Manufacturer		
Vaccine	GlaxoSmithKline	Merck	Sanofi Pasteur
HepB	$4.35	$4.35	
DTaP	$17.75		$17.75
Hib	$5.80	$5.80	$5.80
IPV	$5.80		$5.80
Subtotal	$33.70	$10.15	$ 29.35
Share	46.0%	13.9%	40.1%

market (i.e., which diseases the manufacturer's vaccines provide immunization against), weighted by the production cost of the attendant monovalent vaccine (see Tables 5.3 and 5.4). Together with an assumed $400 million base level of total industry profit, the rule results in the following target profit levels: GlaxoSmithKline, $184 million; Merck, $56 million; Sanofi Pasteur, $160 million.

Many experts provide arguments contending that the current economic return for investing in vaccine development is too low, relative to the benefit immunization programs provide society [18, 28, 38, 45, 46, 50]. It is assumed then, that the CDC may wish to increase industry profit levels in order to provide a financial incentive that improves the long term investment environment for the provision of vaccines. In the results presented in this chapter, two CDC vaccine procurement policy scenarios are evaluated. A sensitivity analysis is performed for each policy scenario where the effect of various industry profit levels on the vaccine system's cost is measured. Cases investigated include increases of 25%, 50%, and 75% over the estimated current industry profit. Table 5.5 reports the different vaccine manufacturer target profit levels examined. Computational results are obtained using TOMLAB®'s suite of MINLP solvers.

Table 5.5: Vaccine manufacturer target profit levels

Case	GlaxoSmithKline	Merck	Sanofi Pasteur
base	$184M	$56M	$160M
+25%	$230M	$70M	$200M
+50%	$276M	$84M	$240M
+75%	$322M	$98M	$280M

5.3.1 Scenario 1 - No Minimum Vaccine Purchase Volumes

Table 5.6 reports the formularies selected by the solver for Scenario 1. Formulary 1 is best described as the Pediarix® dominant formulary since three Pediarix® doses deliver nine of the 16 antigens

required to satisfy the RCIS. Formulary 2 is best described as the Pentacel® dominant formulary since three Pentacel® doses deliver nine of the 16 antigens required to satisfy the RCIS. Both Formulary 1 and Formulary 2 satisfy the RCIS in only eight vaccine doses. The solver has selected the two formularies with the most advantageous structure with respect to the number of injections. Recall that the cost of injection is assumed to be $10.00. This relatively higher value makes combination vaccines like Pediarix® and Pentacel® valuable and cost effective alternatives.

Table 5.6: Vaccine formulary selection (Scenario 1)

Period	Formulary 1	Formulary 2
1	RECOMBIVAX HB®	RECOMBIVAX HB®
2	Pediarix® PedvaxHIB®	RECOMBIVAX HB® Pentacel®
3	Pediarix® PedvaxHIB®	Pentacel®
4	Pediarix®	RECOMBIVAX HB® Pentacel®
5	TriHIBit®	TriHIBit®
6	Kinrix®	Kinrix®

Table 5.7 reports the vaccine system cost and the formulary purchase quantities for Scenario 1. The results indicate that for the base case a birth cohort of 2.3 million children can be immunized according to the 2010 RCIS at an overall vaccine system cost of $662.8 million (note that this cost only considers the four competitive antigens of interest in this chapter). Nearly two million children satisfy the RCIS using Formulary 1. The remaining $300,000$ satisfy the RCIS using Formulary 2. The sensitivity analysis indicates that increasing industry profit by 25% increases vaccine system cost by approximately 15%. The formulary purchase quantities (and vaccine prices) change with each case in order to meet the higher profits required.

Table 5.7: Vaccine system cost and formulary purchase quantities (Scenario 1)

Mfg. Profit	Sys. Cost	Formulary 1	Formulary 2
base	$662.8M	1,993,900	306,100
+25%	$763.3M	1,474,300	825,700
+50%	$863.6M	1,150,000	1,150,000
+75%	$962.9M	1,429,900	880,100

Table 5.8 reports the vaccine prices and purchase quantities for Scenario 1. The results indicate a wide range of possible vaccine prices and quantities are available to meet policy maker criteria. In the base case, nearly six million doses of Pediarix® are purchased while less than one million doses of Pentacel® are purchased. However, Pentacel® is priced at its private sector price of $75.33 while Pediarix® is priced at $31.854. Note that the nonconvex bilinear nature of the price-quantity relationship enables policy makers to specify more tightly defined ranges of vaccine prices and still achieve a minimum cost solution that satisfies the manufacturer profit constraints. It is also

important to note that of the 13 vaccines considered, seven are not purchased. This characteristic may be of concern to policy makers since it may be deemed too risky to stake the success of the entire public immunization program on the successful manufacture, distribution, and delivery of six vaccines; when dependent on so few vaccines, production problems create immediate, acute shortages and may substantially impact immunization coverage levels. Scenario 2 addresses this concern by requiring a minimum purchase level of $500,000$ for all 13 vaccines.

Table 5.8: Vaccine prices and purchase quantities (Scenario 1)

	base		+25%		+50%		+75%	
Vaccine	Price ($)	Doses (M)	Price ($)	Doses (M)	Price ($)	Doses (M)	Price ($)	Doses (M)
Infanrix®	-	0.000	-	0.000	-	0.000	-	0.000
Hiberix®	-	0.000	-	0.000	-	0.000	-	0.000
ENGERIX B®	-	0.000	-	0.000	-	0.000	-	0.000
Kinrix®	16.449	2.300	15.937	2.300	41.540	2.300	39.666	2.300
Pediarix®	31.854	5.982	51.758	4.423	61.023	3.450	62.310	4.260
PedvaxHIB®	11.511	3.988	19.653	2.949	22.145	2.300	22.770	2.840
RECOMBIVAX HB®	6.560	2.912	5.266	3.951	9.037	4.600	10.244	4.060
COMVAX®	-	0.000	-	0.000	-	0.000	-	0.000
Tripedia®	-	0.000	-	0.000	-	0.000	-	0.000
ActHIB®	-	0.000	-	0.000	-	0.000	-	0.000
IPOL®	-	0.000	-	0.000	-	0.000	-	0.000
TriHIBit®	46.346	2.300	46.315	2.300	33.450	2.300	46.346	2.300
Pentacel®	75.330	0.918	47.656	2.477	55.982	3.450	75.330	2.640

5.3.2 Scenario 2 - Minimum Vaccine Purchase Volumes

Table 5.9 reports the formularies selected by the solver for Scenario 2. Formularies 1 and 2 are exactly the same as in Scenario 1. Formulary 3 is best described as the COMVAX® dominant formulary since COMVAX® is administered and together with the use of PedvaxHIB®, the Merck Hib advantage is achieved. The Merck Hib advantage provides Hib coverage for the 2-,4-, and 6-month series in only two doses instead of the three doses needed if other manufacturers' Hib vaccines are used, thereby saving a shot. Formulary 4 is best described as a monovalent formulary (one of many such formularies that could be selected), since every vaccine administered is considered a monovalent vaccine. Formularies 3 and 4 do not have the same inherent structural advantage as Formularies 1 and 2 since they require 13 and 16 vaccine doses, respectively, to satisfy the RCIS. Formularies 3 and 4 are selected in order to satisfy the minimum dosage requirement.

Table 5.10 reports the vaccine system cost and the formulary purchase quantities for Scenario 2. The results indicate that for the base case a birth cohort of 2.3 million children can be immunized according to the 2010 RCIS at an overall vaccine system cost of $703.1 million. The sensitivity analysis indicates that increasing industry profit by 25% increases vaccine system cost by approximately 14%. Regarding the formulary purchase quantities, it is seen that Formularies 1 and 2 are

Table 5.9: Vaccine formulary selection (Scenario 2)

Period	Formulary 1	Formulary 2	Formulary 3	Formulary 4
1	RECOMBIVAX HB®	RECOMBIVAX HB®	ENGERIX B®	RECOMBIVAX HB®
2	Pediarix® PedvaxHIB®	RECOMBIVAX HB® Pentacel®	Infanrix® COMVAX® IPOL®	RECOMBIVAX HB® Tripedia® ActHIB® IPOL®
3	Pediarix® PedvaxHIB®	Pentacel®	Infanrix® PedvaxHIB® IPOL®	Tripedia® ActHIB® IPOL®
4	Pediarix®	RECOMBIVAX HB® Pentacel®	Infanrix® ENGERIX B® IPOL®	RECOMBIVAX HB® Tripedia® ActHIB® ActHIB®
5	TriHIBit®	TriHIBit®	Infanrix® Hiberix®	Hiberix® Tripedia®
6	Kinrix®	Kinrix®	Kinrix®	Tripedia® IPOL®

purchased to minimize cost and meet manufacturer profit requirements. Formularies 3 and 4 are purchased only to satisfy vaccine minimum purchase quantities as they are more expensive. An important implication of the results presented here is that minimum vaccine purchase quantities (and the attendant risk mitigation) is achieved at a relatively small system cost of $40 million ($703.1M vs. $662.8M), an increase of approximately 6%. Using a limited number of inferior formularies to achieve a measure of risk mitigation with respect to the impact of vaccine production interruptions may be cheaper than one would expect.

Table 5.10: Vaccine system cost and formulary purchase quantities (Scenario 2)

Mfg. Profit	Sys. Cost	Formulary 1	Formulary 2	Formulary 3	Formulary 4
base	$703.1M	1,362,700	270,600	500,000	167,700
+25%	$803.1M	1,171,400	461,900	500,000	167,700
+50%	$903.2M	980,000	653,300	500,000	167,700
+75%	$1002.8M	1,088,300	545,000	500,000	167,700

Table 5.11 reports the vaccine prices and purchase quantities for Scenario 2. The results indicate a much more diversified allocation of vaccine purchases when compared to Scenario 1 (see Table 5.8). For example, in the case of 75% increased manufacturer profit, the highest purchasing volume is 3.265 million doses of Pediarix® while the lowest volume is 500,000 doses of COMVAX® and ActHIB®. Regarding vaccine prices, it is important to know that federal law (i.e., the Omnibus Budget Reconciliation Act of 1993) places price caps on many of the monovalents. This price setting restriction keeps the profit margins on these vaccines very low. Consequently, the prices of unrestricted combination vaccines must be greatly increased in order to attain the required manufacturer profit levels. Note that the price caps of TriHIBit® and Pentacel® were relaxed in the +75% case in order to attain a feasible solution.

Table 5.11: Vaccine prices and purchase quantities (Scenario 2)

	base		+25%		+50%		+75%	
Vaccine	Price ($)	Doses (M)	Price ($)	Doses (M)	Price ($)	Doses (M)	Price ($)	Doses (M)
Infanrix®	13.795	2.000	3.550	2.000	5.943	2.000	7.652	2.000
Hiberix®	8.190	0.667	1.450	0.667	4.340	0.667	1.450	0.667
ENGERIX B®	5.060	1.000	1.450	1.000	10.250	1.000	10.244	1.000
Kinrix®	8.607	2.133	22.464	2.133	48.000	2.133	47.995	2.133
Pediarix®	41.572	4.089	60.254	3.514	62.757	2.940	70.711	3.265
PedvaxHIB®	9.067	3.226	22.770	2.843	22.770	2.460	22.766	2.677
RECOMBIVAX HB®	5.613	2.674	1.450	3.057	4.218	3.440	7.240	3.223
COMVAX®	41.095	0.500	18.783	0.500	43.560	0.500	43.560	0.500
Tripedia®	14.250	0.833	14.250	0.833	14.250	0.833	14.250	0.833
ActHIB®	8.830	0.500	8.830	0.500	8.830	0.500	8.830	0.500
IPOL®	11.740	2.167	11.740	2.167	11.740	2.167	11.740	2.167
TriHIBit®	46.346	1.633	46.346	1.633	46.346	1.633	60.000	1.633
Pentacel®	75.330	0.812	75.330	1.386	75.330	1.960	99.999	1.635

5.3.3 Discussion

AMVF3P provides a robust mathematical framework for analyzing and assessing a wide variety of pediatric vaccine pricing and procurement policies. The results presented in this chapter represent a sample of the different policies that can be evaluated in order to gain important insights. Indeed, one fundamental insight reported in this chapter is the relative inexpensiveness of establishing minimum purchasing volume requirements to reduce the risk of vaccine supply interruption negatively impacting immunization coverage levels. It is important to stress that it is the structure of the presented problem that is valuable; users of the tool specify the problem parameters. AMVF3P can be used to design finely tailored policies to meet specific public health policy goals and assist decision makers in crafting policies (in negotiations between government and industry) that address concerns regarding the vaccine system's cost, robustness, and ongoing viability.

5.4 Conclusions

This chapter describes AMVF3P, which seeks pediatric vaccine prices and purchase quantities that ensure a given birth cohort is fully immunized according to a particular childhood immunization schedule at an overall minimum cost while also ensuring vaccine manufacturers each attain an appropriate level of profit. Although AMVF3P was shown to be *NP*-hard, real-world problem instances are sufficiently small and are solvable in a reasonable amount of time using commercial software. The practical value of the proposed MINLP model was demonstrated by analyzing and assessing different pricing and purchasing policies that the CDC could adopt in attempting to actively manage the long-term provision of pediatric vaccines.

Public health policies made by the CDC greatly influence the capital investment environment

within the United States pediatric vaccine market. Current policies regarding vaccine prices and purchase quantities affect pharmaceutical companies' expectations concerning future profit for vaccines still in the developmental stage. An expectation of excessive price control suppresses capital investment in the research and development of new vaccines as pharmaceutical companies see that alternative investment vehicles would provide a higher return on investment. The necessary revenue streams for sustaining the pharmaceutical industry's participation in the vaccine market would be absent, stifling innovation, and ultimately leading to an unsafe environment for the reliable provision of vaccines.

The CDC's vaccine pricing and purchasing policies are critical to the long term success of public immunization programs. Indeed, the CDC has a delicate task: it must balance the division of the net benefit (i.e., economic vs. social surplus) received from the sale and use of a vaccine between the vaccine manufacturer and the purchaser/consumer. The monopsonistic federal government is well positioned to achieve the appropriate balance between immunization coverage levels (facilitated by lower prices) and appropriate investment in research and development (facilitated by higher prices). The AMVF3P MINLP model provides a mathematical framework by which public health policy practitioners at the CDC can develop and analyze any number of potential policies that seek to address this balance and best provide for the common good.

Several potentially important economic factors that could impact the overall cost of immunization are not included in this study. The exclusion of such factors is due primarily to the lack of data or economic models regarding them. Some factors are important as an issue of differentiation between manufacturer products. For example, vaccine efficacy, adverse reaction frequency, shelf life, and thermal storage requirements [31] could all be factors distinguishing two vaccines and may influence the decision on which product to purchase. In addition to product differentiation, this study does not address potential cost savings associated with reduced inventory handling resulting from the reduction in the number of separate vaccines included in the lowest overall cost formulary. Lastly, brand loyalty, volume discounting, risk of shortages, and formulary inertia are not addressed due to the difficulty in quantifying economic model parameters describing them.

CHAPTER 6

CONCLUSIONS

This dissertation applied operations research and game theoretic methods to aid market participants in making more informed decisions regarding the pricing and purchasing of vaccines in the public sector of the United States pediatric vaccine market. The pediatric immunization market was analyzed from three different perspectives.

In Chapter 3 an operations research approach was proposed for analyzing a pharmaceutical company's pricing strategy for a single combination vaccine. Unlike prior operations research papers in the area of pediatric immunization, the proposed approach treated the cost of an injection as a random variable. The main contribution was to provide a methodology for analyzing pricing strategies of directly competing, partially overlapping, and mutually exclusive combination vaccines in the United States pediatric vaccine market, with the goal of maximizing a pharmaceutical company's expected revenue. The resulting analysis showed that Pentacel was not competitively priced when compared to Pediarix, its strongest competitor, for federal contract prices ending 31 March 2010. Accordingly, Sanofi Pasteur should have expected to generate low revenue upon market entry, while Pediarix remained well priced, with GlaxoSmithKline able to generate a high level of revenue at the expense of Sanofi Pasteur. The proposed pricing approach suggests an appropriate price for Pentacel whereby a substantial increase in expected revenue can be realized. It is interesting to note that for federal contract prices ending 31 March 2011 Pentacel dropped in price while Pediarix increased in price. These price adjustments are consistent with the analysis presented - that Pentacel was overpriced relative to Pediarix and an adjustment was needed to make the two dominant vaccine formularies more economically equitable.

In Chapter 4, a game theoretic approach enabled formulation of a static Bertrand pricing model that characterizes oligopolistic interaction between firms in a multiple product homogeneous market. A pure strategy Nash equilibrium was sought to analyze the depicted market. The repeated game version of the model enabled repeated interaction between firms, allowing examination of

tacit collusion in the market of interest. The main contribution was in the treatment of the combinatorial and interdependent nature of the novel demand structure in the market of interest. An iterative improvement algorithm was defined that constructed a pure strategy Nash equilibrium for the static game. Sufficient conditions for the existence of pure strategy Nash equilibria (some in the limiting sense) were provided, indicating that this class of games always yields at least one pure strategy equilibrium. The utility of the models was demonstrated by analyzing the United States public sector pediatric vaccine market. The relevant Nash equilibrium payoffs indicated that engaging in Bertrand price competition resulted in a profound loss of profit for all of the pharmaceutical firms competing in the pediatric immunization market. Certainly, pharmaceutical firms are aware that systematic reductions in price negatively impacts future profits, especially considering the price inelasticity in the market. The equilibrium results of the repeated game provided conditions under which tacit collusion agreements could be upheld. The current vaccine prices and their corresponding adjustments in recent years reflect this understanding.

Possible research extensions include the incorporation of fixed charge costs and capacity constraints. Also, examining the simultaneous treatment of multiple market segments may provide an appropriate analytical perspective for certain markets of interest (e.g., considering both the public and private sector of the pediatric vaccine market). In the context of the repeated game, Γ^r, it may be worthwhile to develop a methodology for determining efficient market sharing allocations. Once the Pareto frontier of efficient allocations (i.e., price points and production levels) are identified, application of Nash Bargaining theory [42] could select an equitable allocation amongst the participating firms. Lastly, uncertainty could be introduced into the model to account for the risk of production interruptions. Often, when determining suppliers, purchasers must consider the risk of shortage and delay.

In Chapter 5, an operations research approach was presented that defined the Altruistic Monopsonist Vaccine Formulary Pricing and Purchasing Problem (AMVF3P) mixed integer non-linear program (MINLP) model, which minimizes the weighted sum of the cost to fully immunize a birth cohort according to a given childhood immunization schedule. The model determines optimal vaccine prices and purchase quantities while ensuring that each vaccine manufacturer earns at least a particular amount of profit, with vaccine production quotas, capacities, and price caps respected. While AMVF3P was shown to be *NP*-hard, real world problem instances are sufficiently small and are solvable in a reasonable amount of time using commercial software. The practical value of

the proposed model was demonstrated by analyzing and assessing different pricing and purchasing policies that the CDC could adopt in attempting to actively manage the long-term provision of pediatric vaccines. The AMVF3P MINLP model provides a mathematical framework by which public health policy practitioners at the CDC can develop and analyze any number of potential policies that seek to best provide for the common good.

Possible research extensions include the development of heuristics for AMVF3P that do not guarantee optimality but execute in time polynomial in the size of the inputs. The determination of approximation bounds and generating empirical results for relevant real-world AMVF3P instances are also of interest.

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