Making Combination Vaccines More Accessible to Low-Income Countries: the Antigen Bundle Pricing Problem

December 1, 2010

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Abstract

Combination vaccines have become the preferred choice for immunizing children in high- and middle-income countries. However, these new vaccines are prohibitively expensive for low-income countries, causing them to rely on older, less-expensive vaccines. This product divergence decreases economies of scale for the purchase of vaccines and eliminates the financial incentive for manufacturers to maintain production of less-expensive vaccines or even to develop new vaccines for diseases affecting developing countries. This paper treats combination vaccines as bundles of antigens that can be priced as a single item. Such bundles are used to formulate an optimization problem that determines the combination vaccine allocation between vaccine producers and different countries under a price discrimination agreement. The objective of the optimization problem is to satisfy countries’ antigen demand at the lowest possible price, while providing a reasonable profit for the vaccine producers. The optimization problem results in a mixed-integer non-linear programming model that simultaneously maximizes the aggregated manufacturing profits and the aggregated customer surplus, and hence, maximizes the total social surplus. Moreover, a constructive heuristic is proposed to determine an approximation to the best allocation of combination vaccines and their range of feasible prices. Computational results show that vaccine prices in all market segments become more affordable as the supply of the most complex combination vaccines becomes more available to low income countries.

1 Introduction

As new vaccines are added to the list of routinely recommended vaccines in different countries, the resulting immunization schedules are becoming more congested [1], with children commonly receiving multiple injections during a single clinic visit. For example, in the United States, a two-month old baby could receive up to five injections in a single clinic visit [2]. An ideal vaccine would be one that provides, in a single injection, all necessary antigens with life-time protection against all diseases [3, 4]. Unfortunately, such an ideal vaccine is not likely to exist, due to biological and manufacturing limitations. However, advances in technology have increased the availability of several of combination vaccines which, in a single dose, provides protection against several diseases.

Until the early 1990s, traditional vaccines were used in industrialized and developing countries, providing low return to vaccine producers. At the time, the global vaccine market size value was just over $USD 2.9 billion [5]. However, the introduction of new combination vaccines has dramatically changed the vaccine market. For vaccine producers, the introduction of new combination vaccines created an opportunity to charge higher prices for their products and improve profit margins. Since vaccine manufacturing capacity is limited [6], there has been a growing trend to produce expensive combination vaccines at the expense of traditional less-expensive vaccines. By the year 2000, the introduction of new combination vaccines caused the global value of the vaccine market to increase to over $USD 6 billion (corresponding to less than 2% of the global pharmaceutical market)[5]. Since then, the global vaccine market size value has increased to $USD 20.5 billion in 2008, and it is expected reach $USD 34 billion by 2012 [7]. However, in 2008, less than 10% of the total market
value corresponded to sales in low- and middle-income countries, and 40% of all global sales volume accounted for only 5% of the global market size value [7]. Furthermore, the introduction of new combination vaccines in developing countries typically occurs only years after these vaccines are introduced in industrialized countries [8]. One of the reasons for such a delay is that different licensing procedures for new vaccines may require the certification of dedicated production facilities, and in order to avoid financial exposure, vaccine manufacturers start building or reconditioning facilities that can supply the minimum vaccine production required to get licensure. Unless manufacturers expand the facilities for new combination vaccines, developing countries may not only face a limited supply of these vaccines, but also of the traditional vaccines whose manufacturing capacity has decreased to accommodate the production of the new combination vaccines [1]. In fact, if it was not for the supply of vaccines produced by non-traditional manufacturers (i.e., companies not affiliated with large multinational pharmaceuticals from industrialized nations), developing countries would face a major vaccine supply crisis (non-traditional vaccine producers supply 86% of the traditional vaccine market [9]). The most critical consequence of the shift in vaccine production practices is the divergence of vaccine product lines between industrialized and developing countries (i.e., vaccines used in industrialized countries are increasingly different than those used in developing countries) [10]. In time, the immunization schedules of industrialized nations could be predominately satisfied by new combination vaccines, which may not be available in developing nations. Milstien et al. [1] claim that an increasing divergence of vaccine product lines may increase production costs (due to reductions in economies of scale), saturate manufacturing capacity, and require more regulatory interventions. Moreover, this increasing divergence of vaccine product lines can reduce the financial incentives for investment in the development and manufacture of vaccines for diseases in developing nations (where most children live) [1, 10, 11]. For example, in 1971, its first year of use, the adenovirus vaccine prevented an estimated 27,000 military hospitalizations of soldiers with acute respiratory disease in the United States armed forces [12]. However, in 1996 the production of the adenovirus vaccine was suspended when the vaccine became economically unattractive for its sole provider [10, 12]. Reductions in the number of vaccines produced for less-profitable markets not only affect developing nations, but also affect nations in profitable markets, since manufacturers have to recuperate their high fixed production and development costs from a smaller customer base. Consequently, in industrialized nations, prices are higher while profits are limited, since a higher portion of the price per dose serves to recover costs.

The introductory price of new vaccines is severely affected by whether or not countries in the different market segments have universal health care services. For example, in the United States, which does not have universal health care, public sector purchasing accounts for over half of the market, yet it is the country where vaccine manufacturers obtain most of their revenue. Additionally, in the United States, vaccine manufacturers often offer price discounts to pediatricians for vaccines, if these are purchased with other pharmaceutical products.

Assuming that combination vaccines could be simultaneously available in all market segments under price discrimination agreements, the question posed in this paper is: At what price should
combination vaccines be offered in each market segment to guarantee vaccine availability in low-profit market segments, and at the same time increase profits for vaccine producers? To answer this question, this paper defines a combination vaccine as an indivisible bundle of antigens and presents an optimization model that maximizes the total social surplus of allocating bundles from vaccine producers to different market segments, where the total social surplus (or total welfare) corresponds to the aggregate profit and customer surplus. This bundle allocation must satisfy the market antigen demand to immunize all its newborn children within their first two years of age. Furthermore, bundle prices should be sufficient to cover production costs, which correspond to the capital-recovery annuities necessary to recover research and development expenses of producing each bundle. Therefore, bundle prices correspond to Ramsey prices, which are prices that maximize social welfare while providing a minimum profit level [13].

The optimization model also includes capacity restrictions and the need to provide an economic incentive to produce and purchase bundles with more antigens. Without loss of generality, all vaccines in an immunization schedule are considered combination vaccines, with monovalent vaccines corresponding to single antigen bundles. The model formulation results in a mixed integer non-linear programming problem (MINLP), which limits its practical application to small-size problems. However, the problem structure allows for the formulation of a constructive algorithm that first solves the allocation of bundles from vaccine producers to market segments, and then solves for the pricing of such allocations.

This paper is organized as follows. Section 2 presents relevant literature on vaccine pricing, bundle pricing, and combinatorial auctions. Section 3 introduces the Antigen Bundling Pricing Problem (ABP) and its formulation. Section 4 discusses the range of prices for which the ABP is feasible for a given bundle allocation. Section 5 describes a heuristic strategy proposed to determine an approximation to the ABP solution. Section 6 presents a computational example, and Section 7 provides concluding comments and directions for future research.

2 Background

Although tiered pricing has been successfully used in the vaccine market since the 1990’s, there has been political pressure (particularly in the United States) to withdraw vaccine producers from tiered pricing arrangements. This is due to the assumption that customers in higher income markets unfairly subsidize vaccine consumption in low-income markets (i.e., developing countries) [14, 15]. For Plahte [8], the use of the term subsidy implies that vaccine prices in industrialized nations are higher than they would have been in the absence of low-price sales to developing countries. However, Plahte [8] claims that this is a misconception, and that tiered pricing in the vaccine market is a win-win-win situation, where producers can benefit from increasing revenues and profits, low-income markets gain access to otherwise inaccessible vaccines, and customers in high-income markets benefit from lower prices. Plahte [8] affirms that introducing new vaccines in low-income markets can reduce the price per dose in industrialized nations, since distributing vaccines to a
larger population can reduce the costs per dose of a vaccine. Danzon and Towse [16] defend the use of tiered pricing for pharmaceutical products and propose the use of Ramsey pricing across different markets in order to cover the high fixed research and development costs for producing pharmaceuticals (i.e., setting prices that maximize social surplus (total welfare) while maintaining a minimum profit [17]).

Vaccine pricing has been studied from different perspectives, ranging from a cost-benefit analysis for the introduction of new vaccines [18], the evaluation of incentives to promote innovation in vaccine research [19, 20, 21], and the design of government interventions in vaccine markets [22, 23, 24, 25]. However, most of these studies have focused on monovalent vaccines. With respect to the pricing of combination vaccines, efforts have focused on evaluating the cost-benefit of introducing such vaccines into the market. For example, Sewell et al. [26, 27] use an iterative bisection search method [28] to determine the maximum inclusion price at which four pediatric combination vaccines could be part of the lowest overall cost formulary (i.e., the selection of vaccines that can satisfy some recommended immunization requirements). The resulting maximum inclusion price is shown to be highly dependent on several factors, including the cost of an injection. Jacobson et al. [29] extend the bisection search method and use Monte Carlo simulation to generate random costs of injections, and then estimate the probability distribution of the maximum inclusion price of the same four combination vaccines. In two further studies, Jacobson et al. [30, 31] analyze the economic value of introducing several combination vaccines [hepatitis B-Haemophilus influenzae type B (HBV-HIB), diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio (DTPa-HBV-IPV), and diphtheria-tetanus-acellular pertussis-Haemophilus influenzae type B-inactivated polio (DTPa-HIB-IPV)].

In marketing and microeconomics, given the growth of e-commerce [32], bundle pricing has received extensive attention. Bundle pricing corresponds to the pricing of a set of products sold in a single bundle. Although examples of bundle pricing are common (e.g., in fast food meals, software applications, telecom services, vacation packages, and downloadable music), no references are available on the use of bundle pricing in pharmaceuticals and vaccines. The early studies in bundle pricing focused on determining under which demand conditions bundle pricing was profitable [33, 34]. More recently, Venkatesh and Kamakura [35] offer normative guidelines in optimal bundling strategies of two products based on their level of complementarity. Salinger [36] suggests that positively correlated reservation prices may increase incentives to bundle in economies of scope (i.e., when the average total cost of production decreases as a result of increasing the number of different goods produced [37]), where the reservation price of an item is defined as the maximum price a customer is willing to pay for such an item.

Little attention was initially given to the actual price determination of different bundles until Hanson and Martin [38] proposed a mathematical programming model to establish the optimal bundle price for all potential bundles that can be offered to customers in different market segments. Most recently, using a multinomial logit model to represent the demand function of the bundle price, Bitran and Ferrer [32] formulate an optimization problem to determine the composition and price
of a bundle that maximizes a company’s expected profit. Their formulation is a MINLP, for which they propose a two-step algorithm. First, they establish the optimal pricing for a bundle, and then they address the optimal bundle selection using dominance properties.

The bundle pricing problem has also been analyzed from the perspective of combinatorial auctions. In a traditional auction, a single item is offered for bid among potential customers and then sold to the winning bidder. In a combinatorial auction, several sets of items are offered as a single item, complicating the customer valuation of the individual bundle components and potentially leading to problems ranging from exposure to collusion. Combinatorial auctions for homogeneous items have been well studied [39, 40, 41], and Vickrey auctions have been shown to ensure an efficient resource allocation for homogeneous items [42]. However, Vickrey auctions for heterogenous bundles are difficult to implement, since bidders are required to reveal their valuation for every possible item combination [42, 43]. For a single seller auction with multiple buyers, Wurman and Wellman [44] present a constructive method for setting bundle prices that ensure the existence of equilibrium prices and an efficient allocation of items. Bikhchandani and Ostroy [45] show that discriminatory, non-linear pricing is necessary to guarantee that competitive equilibria exist in the bundling pricing problem of a single seller.

3 Antigen Bundling Pricing Problem (ABP)

This paper considers a hypothetical vaccine market dynamics, first presented by Proano [46], resulting from the interaction of three types of agents: vaccine producers who supply bundles, market segments that require bundles to satisfy their antigen demands, and a monopsonistic entity (i.e., a buyer with market power such as UNICEF) that behaves as an intermediary between manufacturers and market segments.

The monopsonistic entity is informed by market segments on their respective antigen demands and then calls on their behalf for vaccine producers to offer bundles that could satisfy such demands at the lowest prices. Acting on behalf of vaccine producers, the monopsonistic entity immediately negotiates bundle prices that the market segments could afford to pay, but that would also result in positive profits for the vaccine producers. The monopsonistic entity does not keep any monetary benefit for itself, and is assumed to be altruistic. Moreover, vaccine producers and market segments act only in their own self interests. Thus, there is no collaboration among vaccine producers and market segments, which justifies the existence of the monopsonistic entity. Since the vaccine market is highly regulated, bundles bought by a market segment cannot be re-sold to any other market segment. In the following formulation the monopsonistic entity may seem to act as a centralized planner whose goal is to increase total social surplus by maximizing savings for those purchasing vaccines, and profits for vaccine producers. However, the monopsonistic entity does not enforce bundle prices on the vaccine manufacturers, it only controls the procurement strategy expressed by the number of doses it purchases from vaccine manufacturers to satisfy the demand of each market segment (i.e., a bundle allocation). Moreover, in order to implement such a procurement
strategy, the monopsonistic entity needs to determine if there are viable prices for both producers and market segments that could be used to guide a negotiation process with the vaccine producers.

It is important to mention that in the present vaccine market a unique global monopsonistic entity does not exist. However, national health services can act as local monopsonistic entities, when vaccine procurement is centralized. The closest existing monopsonistic entity, as described in this paper, is the Pan-American Health Organization (PAHO) Revolving Fund, which is the main mechanism through which Latin American and Caribbean countries procure their vaccines. However, PAHO does not use optimization methods to determine the optimal amount of vaccines to purchase. The Revolving Fund operates on an annual cycle where countries establish their annual vaccine requirements for the following year, and then PAHO consolidates these annual requirements, placing bids to international suppliers. When suppliers and prices are determined, the revolving fund averages prices across all sellers for each vaccine and then such average prices are provided to the countries in Latin America and the Caribbean [47]. Finally, PAHO acts as a procurement agent on behalf of the country members, placing quarterly orders to suppliers, specifying amounts, destinations, and shipping dates.

For the following model, it is also assumed that market segments assign different utility values to each bundle, which are reflected in the bundles’ reservation prices. Moreover, no producer sells a bundle at a loss, and no market segment buys a bundle paying more than its reservation price. Furthermore, the cost structure of the vaccine market assumes that variable production costs are negligible compared to the research and development costs. Additionally, since vaccines are produced in large batches [7, 48], the variable production cost per dose is assumed to be insignificant relative to the various manufacturing prices. For example, the production cost per dose of live-attenuated vaccines is on the order of pennies of a $USD, while the cost of pneumococcal conjugate vaccines, which is among the most expensive vaccines to make, is less than $USD 3 per dose [7].

Consider a vaccine market composed of a set of market segments, $M$, with each market segment corresponding to a group of countries with similar income levels and immunization schedules. Assume that each market segment has an antigen demand $A_1(m) \in A$, and it must immunize all its children under two years of age, according to the market segment’s immunization schedule. Furthermore, the set of all vaccine producers in the vaccine market, $P$, can produce a finite set of different bundles, $B$. The following additional notation is used to describe the mathematical formulation of the Antigen Bundling Pricing Problem (ABP).
SETS

A  Set of all antigens
B  Set of all bundles
M  Set of all market segments
P  Set of all vaccine producers

\[ A_1(b) \] Set of antigens provided by bundle \( b \in B \), with \( A_1(b) \subseteq A \)
\[ A_2(m) \] Set of antigens required by market segment \( m \in M \), with \( A_2(m) \subseteq A \)
\[ B_1(a) \] Bundles in \( B \) that supply antigen \( a \in A \), with \( B_1(a) \subseteq B \)
\[ B_2(p) \] Bundles manufactured by producer \( p \in P \), with \( B_2(p) \subseteq B \)
\[ N(b,p) \] Subset of bundles in \( B_2(p) \) that, when combined with each other, supply an equivalent antigen offering to that provided by bundle \( b \in B_2(p), p \in P \)
\[ Q(b,p) \] Set of all possible subset of bundles \( N(b,p) \) for \( b \in B_2(p), p \in P \)

PARAMETERS

\[ R_{bm} \] Reservation price of bundle \( b \in B \) in market segment \( m \in M \)
\[ \lambda_m \] Average number of children born per year in market segment \( m \in M \)
\[ C_{bp} \] Capital-recovery annuity for the production-development cost of bundle \( b \in B \) when manufactured by vaccine producer \( p \in P \)
\[ d_{am} \] Number of doses of antigen \( a \in A \) required to provide full immunity to a child in market segment \( m \in M \)
\[ D_{bm} \] Maximum number of doses of bundle \( b \in B \) that could be administered to a child in market segment \( m \in M \) to avoid overimmunization (i.e., \( D_{bm} = \min\{d_{am} : a \in A_1(b)\} \))
\[ S_{bp} \] Maximum number of doses of bundle \( b \in B \) that can be produced by manufacturer \( p \in P \)
\[ \delta \] Scaling constant used to model vaccine vaccine demand elasticity

VARIABLES

\[ X_{bmp} \] Number of doses of bundle \( b \in B \), supplied by vaccine producer \( p \in P \), offered to market segment \( m \in M \)
\[ Y_{bmp} \] Price per dose of bundle \( b \in B \), supplied by vaccine producer \( p \in P \), offered to market segment \( m \in M \)
\[ \gamma_{bp} \] Binary variable taking value of one if bundle \( b \in B \) is manufactured by vaccine producer \( p \in P \), and zero otherwise.

The ABP is now formally presented,

\textbf{ABP:}
MAXIMIZE

\[
\sum_{p \in P} \sum_{b \in B_2(p)} \sum_{m \in M} R_{bmp} X_{bmp} - \sum_{p \in P} \sum_{b \in B_2(p)} C_{bp} \gamma_{bp}
\]  

SUBJECT TO

\[ (R_{bm} - Y_{bmp}) \gamma_{bp} \geq \left( \sum_{t \in N(b,p)} (R_{tm} - Y_{tpm}) \right) \gamma_{bp} \quad p \in P, \ b \in B_2(p), \ m \in M \]  
and for all \( N(b,p) \subseteq Q(b,p) \)

\sum_{p \in P} \sum_{(b \in B_1(a) \cap B_2(p))} X_{bmp} = d_{am} \lambda_m \quad a \in A, \ m \in M \]

\sum_{m \in M} X_{bmp} \leq \gamma_{bp} S_{bp} \quad p \in P, \ b \in B_2(p) \]

\sum_{m \in M} Y_{bmp} X_{bmp} \geq C_{bp} \gamma_{bp} \quad p \in P, \ b \in B_2(p) \]

\[ X_{bmp} \leq D_{bm} \lambda_m \left( 1 - \left( \frac{Y_{bmp}}{\delta R_{bm}} \right)^\phi \right) \quad p \in P, \ b \in B_2(p), \ m \in M \]

\[ Y_{bmp} \geq Y_{bnp} \quad p \in P, \ b \in B_2(p), \ m \in M \text{ and } R_{bmp} \geq R_{bnp} \]

\[ 0 \leq Y_{bmp} \leq R_{bm} \quad p \in P, \ b \in B_2(p), \ m \in M \]

\[ X_{bmp} \geq 0 \quad p \in P, \ b \in B_2(p), \ m \in M \]

\[ \gamma_{bp} = \{0, 1\} \quad p \in P, \ b \in B_2(p). \]

The objective function (1), maximizes the sum of the total profit and the total customer surplus (in $USD) across all vaccine producers and across all market segments, respectively. Therefore, the total profit corresponds to the aggregated revenue minus the aggregated fixed cost of producing each bundle,

\[
\sum_{p \in P} \sum_{b \in B_2(p)} \sum_{m \in M} Y_{bmp} X_{bmp} - \sum_{p \in P} \sum_{b \in B_2(p)} C_{bp} \gamma_{bp}
\]

The total customer surplus is defined as the aggregate difference between the maximum price customers are willing to pay for a bundle (i.e., its reservation price) and the bundle’s actual selling price. Therefore, the customer surplus for a bundle accounts for the value received by the market
segment for each purchased bundle and is given by

$$\sum_{p \in P} \sum_{b \in B_2(p)} \sum_{m \in M} (R_{bm} - Y_{bmp}) X_{bmp}$$

(12)

Furthermore, no customer would purchase a bundle if the resulting customer surplus is negative. Adding (11) and (12) results in the total social surplus, or total welfare, given by (1). Maximizing the total social surplus is equivalent to increasing the value of the vaccine market. Note that (1) results in an expression that does not depend on the bundle prices, but only on the choice of bundles and the number of doses allocated by vaccine producers to different market segments, $\gamma$ and $X$, respectively.

Constraint (2) indicates that for a vaccine producer, manufacturing a combination vaccine is attractive if customers prefer the combination vaccine over any set of vaccines that could together provide an equivalent antigen protection at a superior customer surplus. Such a customer preference exists when the economic benefit (i.e., customer surplus) of applying the combination vaccine is at least equal to that of applying any possible set of vaccines with an equivalent antigen offering.

Constraint (3) ensures that the vaccine supply satisfies all the necessary antigens required to immunize all children in each market segment. In practice, it may not be feasible to administer bundles without inducing extraimmunization, which is not permitted. If extraimmunization is allowed, then the equality in (3) can be changed to an inequality, which would result in allocations that may not have prices that clear the market. However, extraimmunization could be modeled by artificially increasing the number of children in each market segment by a proportion equivalent to the allowed extraimmunization for each market segment.

The total number of bundles supplied by a vaccine producer must be restricted by the production capacity for such a bundle, which is captured in (4). Producers manufacture only profitable bundles. Hence, the total revenue generated from selling a bundle must be at least equal to an annuity necessary to recover production and development costs, as captured in (5).

The bundle demand is bounded above by a function of its selling price, as captured in (6), which suggests that price elasticity (i.e., the ratio between the change in quantity demanded for a product and the product’s change in unit price) is not constant, resulting from the societal importance of vaccines. In fact, the model assumes that price elasticity increases gradually as prices increase. Therefore, bundle demand is more affected by price increments when the bundle’s price is relatively high compared to its reservation price. Note that for $\phi = 1$, constraint (6) corresponds to a linear demand function commonly used in the economics literature. Any $\phi > 1$ suggest a concave polynomial function.

Constraint (7) guarantees that if a bundle is offered in multiple market segments, the price of the bundle is larger in the market segments with higher reservation price. Constraint (8) ensures that the price of a bundle offered to a market segment will be lower than its reservation price in such a market. Constraint (9) enforces nonnegative conditions for both bundle quantities and bundle prices. The binary variables $\gamma_{bp}$ for all $p \in P$, $b \in B_2(p)$ denote whether or not a bundle is
produced.

Note that since information about the variable production costs per dose is highly confidential, it is assumed that producers would be reluctant to share such information with the monopsonistic entity. However, if variable costs were to be included in the ABP, the objective function would be modified, resulting in equation (1) minus the sum of variable production costs across all bundles and producers. With regards to the feasible region, the right-hand side of constraint (5) will have to include the total production cost of the corresponding bundle.

4 Solving the ABP

The ABP is a difficult problem to solve. Proano [46] proved that an arbitrary instance of the single-sink, fixed-charge transportation problem (SSFCTP) [49], which is NP-hard, can be reduced to a particular instance of the ABP, and hence, the ABP is NP-hard. Additionally, the ABP is a mixed integer non-linear programming problem, which limits its practical application to small-size problems. Furthermore, due to the concave nature of constraint (6) (for $\phi > 1$) optimality cannot be guaranteed. Additionally, because of its objective function (1), the ABP provides a bundle allocation that maximizes the total social surplus, and with a set of feasible prices to the ABP constraints for the given allocation. The following section describes how to determine the range of feasible prices that maximize total social surplus for the bundle allocation that solves the ABP, given by the vectors $X^*$ and $\gamma^*$.

4.1 Determining the range of feasible prices for a bundle allocation

Given a bundle allocation that maximizes the total social surplus, $X^*$ and $\gamma^*$, the upper bound on their corresponding feasible prices, $Y^*$, can be obtained by maximizing the total profit (i.e., equation (11)) subject to all ABP constraints. The problem is solved considering the bundle allocation given by $X^*$ and $\gamma^*$ as input data rather than a set of decision variables. Similarly, the lower bound of the feasible bundle prices $\overline{Y}^*$ can be obtained by maximizing the total customer surplus (i.e., equation (12)) subject to all ABP constraints, and when the bundle allocation is also considered input data. For convenience, the optimization problem of determining the upper bound of the feasible bundle prices is referred as $\text{ABP-PF}(X^*, \gamma^*)$, since the problem maximizes the total profit, while the optimization problem of determining the lower bound of the feasible bundle prices is referred as $\text{ABP-CS}(X^*, \gamma^*)$ since it maximizes the total customer surplus. It is important to note that $\text{ABP-PF}(X^*, \gamma^*)$ and $\text{ABP-CS}(X^*, \gamma^*)$ are linear programming problems.

The definitions of $\text{ABP-PF}(X^*, \gamma^*)$ and $\text{ABP-CS}(X^*, \gamma^*)$ are used in Theorem 1 to characterize the family of solutions that provide the same total social surplus provided by the ABP feasible bundle allocations $X^*$, $\gamma^*$.

**Theorem 1:** Given an ABP feasible allocation, $X^*$ and $\gamma^*$, let $\overline{Y}^*$ and $\underline{Y}^*$ be the optimal solutions to problems $\text{ABP-PF}(X^*, \gamma^*)$ and $\text{ABP-CS}(X^*, \gamma^*)$ when the bundle allocation and the choice of
bundle production is fixed to \( X^* \) and \( \gamma^* \), respectively. Then, any set of bundle prices, \( Y^* \), resulting from the linear convex combination of \( \overline{Y}^* \) and \( \underline{Y}^* \), solves the ABP and results in the total social surplus obtained at \( X^* \) and \( \gamma^* \).

Proof. See Appendix.

Based on Theorem 1, Figure 1 depicts how to obtain the range of feasible prices for an ABP allocation.

5 Constructing an approximate ABP solution

The ABP formulation presented in Section 3 is a MINLP optimization problem with non-convex constraints, for which the computational time increases faster than the increase in the number of decision variables. The following constructive heuristic determines an approximation to the best bundle allocation by solving a sequence of relaxed ABP problems. Then the resulting bundle allocation can be used as an input for the algorithm described in the previous section 4.1, in which the problems ABP-PF(\( X^*, \gamma^* \)) and ABP-CS(\( X^*, \gamma^* \)) are solved to determine the range of prices for which the bundle allocation is feasible.

5.1 Approximating the best bundle allocation

Since the total social surplus (1) simultaneously maximizes both (11) and (12), those bundles with the highest potential of increasing profit and customer savings will contribute the most towards the total social surplus value. Such bundles correspond to those vaccines with higher reservation prices on all markets and relatively lower research and development annuity costs. Therefore, the following heuristic provides an approximation to the best ABP bundle allocation by sequentially solving ABP-R(i), which is a relaxed version of the ABP when only one bundle, i, is available at the time. The sequence of ABP-R(i) problems is solved starting with those bundles with highest potential contribution to the total social surplus. Such a contribution for a bundle is given by the ratio between the sum of its reservation prices across all market segments and its research and
development costs. For each one-bundle-at-a-time problem, the resulting bundle allocation is used as an input parameter for the next problem, hence reducing its size. Figure 2 depicts details for the proposed heuristic

\[ r(i) = \sum_{m \in M} \frac{R_{im}D_{im}}{C_p} \quad i \in B_2(p) \]

Figure 2: Heuristic to approximate the best bundle allocation

5.1.1 ABP-R(i)

The ABP-R(i) problem determines the allocation of polyvalent bundle \( i \in PB' \) that myopically maximizes its total social surplus under a relaxed demand constraint. The ABP-R(i) corresponds to the ABP problem of Section 3, subject to the constraints (2), (4) to (9), and with the following demand constraint replacing constraint (3):

\[ \sum_{p \in P:i \in B_2(p)} \left( \sum_{(i \in B_1(a) \cap B_2(p))} X_{imp} \right) \leq d_{am}\lambda_m \quad a \in A, \ m \in M \] (13)

6 Computational Results

This section reports computational results that illustrate the application of the ABP and its constructive heuristic to a hypothetical vaccine market. A series of computational experiments describe the impact of restricting vaccine access to different markets segments based on their relative income levels, and also the effect of increasing the supply of the most complex bundle. All scripts used in this section are implemented in AMPL using the KNITRO 6.0 solver.

The data example for this section consists of a hypothetical vaccine market composed of four market segments, each having immunity requirements for Diphtheria, Pertussis, Tetanus, Hepatitis B, Haemophilus Influenzae type B, and Polio. There are three vaccine producers satisfying these antigen needs by supplying vaccines through all of the 15 possible antigen combinations. Therefore, it is assumed that all 15 bundles can be manufactured. Figure 3 displays the bundles supplied by each of the vaccine producers, considering that the vaccine producers have a mutually exclusive
bundle offering, through which each supplies all antigens required in a market. This product offering mimics a common practice in some vaccine markets (e.g., USA), where typically producers do not compete offering bundles with exactly the same antigen content.

The market segments result from classifying 161 countries into high, middle, low, and poorest income countries, based on their gross national income, using information from the World Health Organization/UNICEF Immunization Summary Report 2007 [50] and the International Monetary Fund [51]. Features of the market segments are summarized in Figure 5, and the list of countries in each market segment is provided in Figure 12 in the appendix. The value of the annuities that account for the research and development costs of the 15 vaccines are assumed to provide 15% return on investment on the total research and development expenses over a 20-year period, in which the average market interest rate is 5%. The actual research and development expenses for the most complex combination vaccines are hypothetical, and their order of magnitude are based on public comments provided by the former President of Wyeth Vaccines, in 2002 [10]. We assume that for the most complex bundles, these costs are approximately $USD 800M. Reservation prices for the high-income market segment are estimated to be $USD 10 above the U.S. federally negotiated vaccine prices [52], and a 1/4, 1/10 and 1/30 of such prices for the middle-income, low-income, and poorest market segments, respectively. Moreover, in order to guarantee a feasible solution for these examples, the reservation prices are such that if vaccines are priced at these values, constraint (2) remains satisfied. Additionally, the supply for monovalent vaccines is assumed to be larger than that for bi-valent vaccines, which is assumed larger than the supply for tri-valent vaccines, and so forth. It is also assumed that there are enough vaccines to satisfy all antigen needs for all newborn children in the four market segments. Combination vaccines that do not contain DTaP and have more than one antigen are assumed to be less available than other vaccines with the same number of antigens. The complete list of parameters used in the data example is presented in Figures 4, 5, and 6. Additionally, the assumed values of $\delta$ and $\phi$ used in constraint (6) are 1.1 and 5, respectively.

<table>
<thead>
<tr>
<th>Vaccine Producer 1</th>
<th>Vaccine Producer 2</th>
<th>Vaccine Producer 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DTaP</td>
<td>2 HBV</td>
<td>3 Hib</td>
</tr>
<tr>
<td>4 IPV</td>
<td>5 DTaP-HBV</td>
<td>6 DTaP-Hib</td>
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<tr>
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<tr>
<td>13 DTaP-HiB-IPV</td>
<td>14 HBV-HiB-IPV</td>
<td>15 DTaP-HBV-Hib-IPV</td>
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</tbody>
</table>

Figure 3: Bundles supplied by each vaccine producer

Figures 7 and 8 compare the bundle allocations obtained by solving the ABP problem for the experimental scenario using the MINLP formulation presented in Section 3 with those obtained via the constructive heuristic presented in Section 5; results are shown for a low (50M doses) and a high supply (175M doses) level of the most complete bundle (i.e., bundle 15; DTaP+HBV+HiB+IPV). Clearly, the resulting ABP bundle allocations are comparable for both the pure MINLP formulation and the constructive heuristic. However, those obtained via the constructive heuristic provide a total social surplus 0.07% smaller of bundle allocation obtained by solving the original ABP.
Furthermore, the solution of the constructive heuristic was obtained in $1/300$th of the time needed to solve the original ABP. For each resulting bundle allocation, Figure 7 and 8 show (in logarithmic scale) the upper and lower bound of its range of feasible prices. These price ranges are broader for high income market segments than those for low income market segments, which indicates that the monopsonistic entity has more latitude negotiating vaccine prices for high income market segments than for low income market segments.

Typically, vaccine producers commercialize combination vaccines in non-industrialized nations years after they began commercialization in industrialized nations. In order to study the consequences of such practice in the proposed computational example, a second experiment applies the constructive heuristic to solve the ABP for different bundle access scenarios. Table 9 describes five scenarios in which bundles, based on their valency, are restricted to particular market segments. Scenario 1 is the most restrictive, limiting the access of four-antigen bundles only to the richest market segments, while scenario 5 is the least restrictive, in which all markets have access to all bundles. The results show that the total social surplus increases when complex bundles are simultaneously offered to high and low income market segments. Figure 10 describes how the total social surplus, the total profit, and the total customer surplus change for the different access scenarios for a given supply of bundle 15. Figure 10 also shows that the total social surplus monotonically increases as scenarios become less restrictive, for instance the total social surplus of scenario 5 is
Antigens | No. Doses
--- | ---
DTaP | 5
HBV | 3
HiB | 4
IPV | 4

Figure 6: Immunization schedule: doses needed to provide full immunization

8% higher than that for the most restrictive scenario. Limiting bundle access results in a more restrictive ABP, and hence, in a smaller feasible region. Therefore, the total social surplus for scenario 5 results in an upper bound of the total social surplus of any other restrictive scenario. Figure 10 also shows that the total customer surplus drives the growth of total social surplus, as vaccine access becomes less restrictive. The total profit received by all manufacturers slightly increases for scenario 2 and then decreases slowly for less restrictive scenarios. These results partially explain why vaccine producers are, in general, reluctant to launch vaccines in all market segments. However, the reduction in total profit between the less restrictive and the most restrictive scenarios is less than 3%.

Using the notation presented in Section 3, the supply for DTaP-HBV-HiB-IPV, corresponding to bundle 15 and produced by manufacturer 3 (the most complete combination vaccine), is referred as $S_{15,3}$. Figures 11 depicts how the total social surplus, total customer surplus, and total profit change when the supply for bundle 15, $S_{15,3}$, increases under scenario 5.

Figure 11 shows that the total social surplus increases as the supply of the more complex bundle increases; this increase is driven primarily by the growth in total customer surplus. Since the range

![Figure 7: Bundle allocations and range of feasible prices (Supply of bundle 15: 50M)]
of feasible prices for the optimal bundle allocations is larger for richer market segments, when the supply of the most complex bundle increases, the growth in total social surplus results from richer market segments paying less for the bundles they consume. The aggregate total profit for all vaccine producers decreases as bundle 15 is more available and affordable. The profit lost for manufacturers whose vaccines are cannibalized by bundle 15 is larger than the profit gained by the producer of bundle 15. For market segments 1, 2, and 3, as $S_{15,3}$ increases, their immunization schedules change and increasingly use more doses of bundle 15. As the richer market segments (1 and 2) purchase more doses of bundle 15, poorer market segments (3 and 4) gain access to doses of other bi-valent and tri-valent combination vaccines that were used by markets 1 and 2 when $S_{3,15}$ is low. Therefore, the purchase of these bi-valent and tri-valent combination vaccines drops and then levels off when the supply of bundle 15 saturates the market. In general, a larger supply of bundle 15 reduces the number of vaccines needed by the market segments to satisfy their immunization needs. This is most evident in markets 2 and 3 after the supply for bundle 15 exceeds 150 million doses.

Computational results also indicate that increasing the supply of the most complex combination vaccines does not necessarily cannibalize the use of the simplest combination vaccines. In fact, a supply of these vaccines is indispensable to facilitate the configuration of feasible immunization schedules. In all market segments, the consumption of the simpler bundles (1, 2, 3, and 4) decreases as the supply of bundle 15 increases; however, when the supply of bundle 15 reaches 175 million doses, the demand for bundle 1 increases, since the bundle 15 can only be used up to 3 times to immunize a child, resulting in a need for 2 additional doses of DTaP (bundle 1).
## Conclusion

This paper presents a MINLP problem for determining the number of bundles and the range of prices for such bundles that simultaneously maximize total profit and total customer surplus. A constructive heuristic is proposed for determining an approximation to the optimal solution of the problem. The heuristic iteratively solves small ABP problems to determine allocations, one bundle at a time, and then solves an ABP for the monovalent vaccines to satisfy any remaining antigen demand. The results reported suggest that organizations such as the World Health Organization (WHO), Pan American Health Organization (PAHO), and UNICEF may serve as trusted intermediaries that could determine actions and policies to simultaneously encourage the development of more complex and innovative vaccines and improve vaccine availability in developing countries, if these organizations determine the vaccine allocations to different market segments. Consequently, through collaboration with vaccine producers and public health decision makers, the intermediary could influence producers when to introduce new vaccines in developing countries, and negotiate profitable and affordable prices. Dealing with the trusted intermediary could also help vaccine producers establish an adequate supply level for all vaccines. Moreover, treating vaccine pricing systemically could facilitate the implementation of future purchasing commitment agreements for new vaccines. For example, the intermediary could use the ABP to determine the minimum price required for a bundle allocation so that it becomes affordable by particular market segments. The results of this paper can be extended to analyze conditions and methods to define when tiered pricing is a feasible strategy for strengthening vaccine supply, and also to quantify

### Figure 9: Bundle access scenarios for different market segments

<table>
<thead>
<tr>
<th>Market Segment</th>
<th>Types of Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-Antigen</td>
</tr>
<tr>
<td></td>
<td>Bundle 15</td>
</tr>
<tr>
<td><strong>Scenario 1</strong></td>
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<tr>
<td>High Income</td>
<td>✓</td>
</tr>
<tr>
<td>Middle Income</td>
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<td>Low Income</td>
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<td>Poorest Countries</td>
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<tr>
<td><strong>Scenario 2</strong></td>
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</tr>
<tr>
<td>High Income</td>
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</tr>
<tr>
<td>Middle Income</td>
<td>✓</td>
</tr>
<tr>
<td>Low Income</td>
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<tr>
<td><strong>Scenario 3</strong></td>
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<td>High Income</td>
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<td>Middle Income</td>
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<td>Low Income</td>
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<tr>
<td>Poorest Countries</td>
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<tr>
<td><strong>Scenario 4</strong></td>
<td></td>
</tr>
<tr>
<td>High Income</td>
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</tr>
<tr>
<td>Middle Income</td>
<td>✓</td>
</tr>
<tr>
<td>Low Income</td>
<td>✓</td>
</tr>
<tr>
<td>Poorest Countries</td>
<td>•</td>
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<tr>
<td><strong>Scenario 5</strong></td>
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<tr>
<td>Low Income</td>
<td>✓</td>
</tr>
<tr>
<td>Poorest Countries</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓ indicates the market segment has access to the vaccine; • otherwise.
manufacturing incentives to subsidize vaccines for less-profitable markets.

To analyze the vaccine subsidy problem, which looks for the minimum financial incentive necessary to introduce a particular bundle into a specific low-income market segment, the ABP could be modified to find the smallest reduction in the bundle’s capital-recovery annuity such that the bundle is selected for a given market. This reduction in the capital-recovery annuity over the development-recovery period would correspond to the minimum subsidy.

The proposed constructive heuristic allows larger ABPs to be solved that could potentially consider all vaccine producers and all their available vaccines, when each country could be considered a market segment. The solution of such a problem could help design and customize specific national public health interventions.

Future research is needed to explain the interaction between vaccine producers, market segments, and the monopsonistic entity. For example, the relationship between vaccine producers and the monopsonistic entity could be represented by a constrained Cournot game, where vaccine producers compete for quantities that maximize their profit under some antigen demand. Similarly, the relationship between the monopsonistic entity and the different market segments can be posed as a set of auctions, where market segments bid for the bundles, given some demand constraints. Understanding such interactions could help determine adequate mechanisms to obtain bundle allocations and prices that are in the best interest of both vaccine producers and market segments. Such a price equilibrium could result in a more sustainable vaccine market.

Acknowledgements

The authors would like to thank Dr. Luciano de Castro from the Department of Economics at the University of Illinois for his useful comments and suggestions, and Dr. Margaret Coleman from the
Figure 11: Evolution of the TSS, TCP, and TP for increasing supply of bundle 15

Centers for Disease Control and Prevention (CDC) for her feedback and clarifying comments about the vaccine market. This research has been supported in part by the National Science Foundation (DMI-0457176).

Appendix

Proof of Theorem 1. 

Since problems ABP-PF($X^*, \gamma^*$) and ABP-CS($X^*, \gamma^*$) use the the vectors $X^*$ and $\gamma^*$ as input parameters, and since total social surplus only depends on $X^*$ and $\gamma^*$, the price vectors $Y^*$ resulting from ABP-PF($X^*, \gamma^*$) and ABP-CS($X^*, \gamma^*$), respectively, do not affect total social surplus.

Next, it is shown that any convex combination of $Y^*_{bmp} \in Y^*$ and $Y^*_{bmp} \in Y^*$ satisfies constraints (2), (5), (6), (7), and (8) and is a feasible solution for ABP.

Since both $Y^*_{bmp}$ and $Y^*_{bmp}$ satisfy constraint (2), then for $\gamma^*_{bp} = 1$

$$R_{bm} - Y^*_{bmp} \geq \sum_{t \in N(b,p)} (R_{tm} - Y^*_{tpm}) \quad \text{for all } p \in P, \ b \in B_2(p), \ m \in M$$

$$R_{bm} - Y^*_{bmp} \geq \sum_{t \in N(b,p)} (R_{tm} - Y^*_{tpm}) \quad \text{and for all } N(b,p) \subseteq Q(b,p)$$

Multiplying both sides of these inequalities by positive constants $\alpha$ and $(1 - \alpha)$, where $0 \leq \alpha \leq 1$,
and adding the left hand sides and right hand sides of the resulting inequalities leads to

\[
R_{bm} - \left( \alpha Y_{bmp}^* + (1 - \alpha) Y_{bmp}^* \right) \geq \sum_{t \in N(b,p)} \left( R_{tm} - \left( \alpha Y_{tpm}^* + (1 - \alpha) Y_{tpm}^* \right) \right)
\]

(14)

for all \( p \in P, b \in B_2(p), m \in M \) and for all \( N(b,p) \subseteq Q(b,p) \), which shows that any convex combination of \( Y_{bmp}^* \) and \( Y_{bmp}^* \) satisfies constraint (2).

Similarly, since both \( Y_{bmp}^* \) and \( Y_{bmp}^* \) satisfy constraint (5), multiplying the resulting constraint inequalities by \( \alpha \) and \( (1 - \alpha) \), where \( 0 \leq \alpha \leq 1 \), and adding the left hand sides and right hand sides of the resulting inequalities leads to

\[
\sum_{m \in M} \left( \alpha Y_{bmp}^* + (1 - \alpha) Y_{bmp}^* \right) X_{bmp}^* \geq C_{bp},
\]

where \( \gamma_{bp}^* = 1 \). Therefore, any convex combination of \( Y_{bmp}^* \) and \( Y_{bmp}^* \) satisfies constraint (5).

Solving constraint (6) for the upper and lower bound of the bundle prices results in

\[
Y_{bmp}^* \leq \delta R_{bm} \left( 1 - \frac{X_{bmp}^*}{D_{bm} \lambda_m} \right)^{\frac{1}{\alpha}} \quad p \in P, b \in B_2(p) \text{ and } m \in M
\]

and

\[
Y_{bmp}^* \leq \delta R_{bm} \left( 1 - \frac{X_{bmp}^*}{D_{bm} \lambda_m} \right)^{\frac{1}{\alpha}} \quad p \in P, b \in B_2(p) \text{ and } m \in M.
\]

Multiplying these last two inequalities by \( \alpha \) and \( (1 - \alpha) \), where \( 0 \leq \alpha \leq 1 \), and then adding the corresponding left hand sides and right hand sides gives

\[
\alpha Y_{bmp}^* + (1 - \alpha) Y_{bmp}^* \leq \delta R_{bm} \left( 1 - \frac{X_{bmp}^*}{D_{bm} \lambda_m} \right)^{\frac{1}{\alpha}} \quad p \in P, b \in B_2(p), m \in M.
\]

Solving for \( X_{bmp}^* \) leads to

\[
X_{bmp}^* \leq D_{bm} \lambda_m \left( 1 - \left( \frac{\alpha Y_{bmp}^* + (1 - \alpha) Y_{bmp}^*}{\delta R_{bm}} \right)^{\phi} \right) \quad p \in P, b \in B_2(p), m \in M
\]

Therefore, any convex combination of \( Y_{bmp}^* \) and \( Y_{bmp}^* \) also satisfies constraint (6).

Since both \( Y_{bmp}^* \) and \( Y_{bmp}^* \) satisfy constraint (7), then multiplying the resulting constraint inequalities by \( \alpha \) and \( (1 - \alpha) \), where \( 0 \leq \alpha \leq 1 \), and then adding the left hand sides and right hand
sides of the resulting inequalities leads to

\[ \alpha \overline{Y}_{bmp} + (1 - \alpha) \overline{Y}_{bmp} \geq Y_{bmp} \quad p \in P, \ b \in B_2(p), \ m \in M, \text{ and } R_{bmp} \geq R_{bmp}. \]

Therefore, any convex combination of \( \overline{Y}_{bmp} \) and \( \overline{Y}_{bmp} \) also satisfies constraint (7).

A similar argument shows that any convex combination of \( \overline{Y}_{bmp} \) and \( \overline{Y}_{bmp} \) also satisfies constraint (8), so that

\[ \alpha \overline{Y}_{bmp} + (1 - \alpha) \overline{Y}_{bmp} \leq R_{bmp} \quad p \in P, \ b \in B_2(p) \text{ and } m \in M. \]

Since any convex combination of \( \overline{Y}_{bmp} \) and \( \overline{Y}_{bmp} \) is feasible to the ABP and maximizes total social surplus, it provides an alternative optimal solution to the ABP.

\[ \square \]

**Market Segments Composition.**

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<tr>
<th>High Income</th>
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Figure 12: Countries in each market segment

**References**


