Omega 40 (2012) 53–64

Contents lists available at ScienceDirect

Omega

journal homepage: www.elsevier.com/locate/omega

Making combination vaccines more accessible to low-income countries: The antigen bundle pricing problem ☆

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ARTICLE INFO

Article history:
Received 2 July 2010
Accepted 24 March 2011
Available online 9 April 2011

Keywords:
Operational/OR
Operations management
Optimization
Bundle pricing
Vaccines
Health care
Price discrimination
MINLP
Heuristics
Vaccine pricing
Combination vaccines
Subsidies

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 maximizes the sum of manufacturing profits and the customer surplus, and hence, it 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 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 to 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

☆ This manuscript was processed by Associate Editor Geunes.

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doi:10.1016/j.omega.2011.03.006

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 (ABP) problem 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 1990s, 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 [19–21], and the design of government interventions in vaccine markets [22–25]. 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.