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Procuring Pediatric Vaccines in a Two-Economy Duopoly

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Abstract

In this work, we aim to present an optimization model for vaccine pricing in a two-economy duopoly. This model observes the price dynamics between a high income country and a low income country that procure vaccinations through PAHO. This model is formulated to provide insights on optimal pricing strategy for PAHO to ultimately increase vaccine accessibility to low income countries. The objective is to satisfy the public demand at the lowest price possible, while providing enough profit for the vaccine manufacturers to stay in business. Using non-linear integer programming, the model results show that cross-subsidization occurs in PAHO vaccine procurement.

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Chapter 1

Introduction

The development of vaccines has been one of the most successful public health instruments of the past century. Implementation of vaccines prevents approximately 2.5 million child deaths around the globe annually as well as millions of more diseases and illnesses (Centers for Disease Control and Prevention, 2014). It has successfully eradicated several diseases, such as smallpox, saving millions of lives annually.

The Pan-American Health Organization (PAHO) is an international public health agency serving as the regional office for the Americas of the World Health Organization (WHO). With the establishment of PAHO Revolving Fund (RF), PAHO has been serving as a vaccine procurement agent on behalf of 41 member countries and territories in the Caribbean and Latin America, delivering 211 million doses as well as managing a pediatric vaccine program responsible for 8.2 million births annually. PAHO is responsible for the negotiation process between the member states and the suppliers for vaccine products. In 2019, RF is working with more than 120 million USD on global immunization. RF creates economies of scale and achieves a strong purchasing power through buying in bulk at the lowest price. According to WHO's Global Vaccine Market Report in 2018, the procurement mechanism has an evident benefit on price. Compared to the self-procured vaccinations, vaccines delivered through PAHO RF are around 48% lower in price per dose (World Health Organization, 2019).

Because PAHO expands the market size by purchasing large amounts of vaccines and distributing at a lower cost for national vaccination programs, PAHO has significant leverage in negotiating the price from the manufacturers. While procuring millions of vaccinations for many countries at a lower cost, PAHO must stay within each nation's vaccination budget, and guarantee a satisfactory profit for the manufacturers to stay in business. With these constraints, we ask the question: From a public organization's perspective, specifically PAHO in this case, what are the best pricing decisions for these vaccinations, while meeting all the aforementioned requirements? Moreover, how does vaccination procurement for multiple countries affect the pricing dynamics?

In this context, the framework of game theory is appropriate. The study of *game theory* entails a mathematical method of decision-making between several parties or players to obtain an optimal, or the "best" solution. The players of the game include manufacturers that produce vaccinations and PAHO who purchases the vaccinations from these manufacturers. The objective of the game is to gain practical insights for optimal pricing strategy for PAHO, while satisfying the specific constraints.

We utilize *non-linear integer programming*, a type of mathematical programming, to obtain the solution to this problem. The non-linearity comes from the objective function and its constraints. *Mathematical programming* is a technique for identifying a function-maximizing solution over a constrained set of feasible values. A model for mathematical programming would be comprised of decision variables representing the problem, an objective function describing the quality of the solutions, and constraints. For this particular problem, the goal is to develop a mathematical program that incorporates the government, or PAHO, as an active player in the vaccination pricing game.

The thesis is structured as follows: Chapter 2 introduces the detailed background and motivation for this study. In addition, it includes relevant game theory concepts, frameworks as well as previous research that help set up the foundation for the developing model. Chapter 3 presents the optimization model. Chapter 4 is the application of the optimization model to a real case study in order to validate the model. Chapter 5 discusses the results of the case study from the previous chapter. Chapter 6 is the conclusion and it discusses limitations of the model and further studies.

Chapter 2

Background

This chapter provides the background information pertinent to the study. Section 2.1 delineates the annual vaccination procurement process for PAHO. Section 2.2 explains some key game theory frameworks that are applied to the model. Lastly, Section 2.3 provides brief summaries of the previous studies that offer foundations for my model.

2.1 PAHO's Vaccination Procurement Process

Through its annual vaccine and syringe demand forecasting, PAHO RF consolidates the requirements for all participating states into one regional order for each vaccination (PAHO, 2019b). This way, the suppliers are presented with a bulk order for the products, making the bidding process more effective. All prices offered by the suppliers are averaged for each product to maintain equity and reported to the member states. This allows the member states to secure their national vaccine procurement budgets by offering the lowest price possible for every product. In order to guarantee a timely and sustainable supply, PAHO selects at least two suppliers based on the quantity and the lowest price offered in the bidding process as well as the the supplier's quality and service record. It also takes into consideration if the selection will promote competition and will not interfere with other national programs (PAHO, 2019a). As the vaccination market is dominated by only few manufacturers, the selection of manufacturers and vaccine prices are crucial to mitigating the high risk of monopolies, which may lead to unreasonable price increase in the vaccines.

2.2 Game Theory

Oligopoly theory is the study of the markets dominated by a small number of sellers. This field can be well-applied to the vaccination market in which only few big manufacturers comprise the game. In this work, we analyze a *duopoly* in which there are only two manufacturers for the game. When the firms are making simultaneous decisions - rather than sequential - to maximize their own profit, the game can be modelled as either a *Bertrand game* or a *Cournot game* (Yue et al., 2006). While the decision variable in a Cournot game is the quantity, a Bertrand game treats the price as a strategic variable.

The vaccination market, specifically the pricing of vaccinations, has been analyzed in various ways through research and optimization. The pricing system was initially analyzed in a static Bertrand oligopoly game in (Robbins et al., 2010). The Bertrand game is a good framework for modelling vaccination pricing as the vaccination prices are newly negotiated every year prior to the purchase (Robbins et al., 2010). However, the Bertrand game does entail three assumptions: first, it assumes unlimited manufacturing capacities, meaning that each manufacturer can satisfy all of market demands. The second assumption is no product differentiation. In other words, all products are interchangeable and substitutable. Lastly, it assumes a game in a *static competition*, which refers to a single independent interaction between the manufacturers, and the choices of a manufacturer does not influence that of others (Behzad and Jacobson, 2016).

These assumptions do not always hold in a practical application in the market. In order to eliminate these unrealistic constraints, a *Bertrand-Edgeworth-Chamberlin competition* is introduced. A Bertrand-Edgeworth game describes the price game of a duopoly in which two manufacturers have limited capacity, relaxing the first assumption. A Chamberlin competition allows for non-homogeneous products, as is the case for the pediatric vaccine market. To summarize, the Bertrand-Edgeworth-Chamberlin competition relaxes the first two assumptions of the Bertrand model, and thus reflects the realistic conditions of the pediatric vaccination market. A *Nash equilibrium* is an optimal solution to the game in which no player has an incentive to deviate from the initial strategy.

2.3 Previous Work and Motivation for the Extended Study

Previous work by Behzad et al. (2015) examine the U.S. pediatric vaccine market using the Bertrand-Edgeworth-Chamberlin framework. The research captures the existence of a unique equilibrium in a market with symmetric and capacity-constrained manufacturers. The *symmetry* in manufacturing capacities refers to equal production capacities in all manufacturers. The study also assumes a linear *demand curve* for each market where the product prices and purchased quantities are inversely proportional. The product is also limited to *monovalent vaccines* - rather than *combination vaccines* - which immunize against exactly one pathogen. Because the combination vaccines in the market do not necessarily immunize against the same set of multiple pathogens, this study does not include the analysis for combination vaccines. Behzad et al. proceed to apply the equilibrium in three different scenarios in the vaccine market. The research continues and successfully eliminates its constraints of symmetry, rendering the model applicable to asymmetric manufacturing capacities (Behzad and Jacobson, 2016). The study concludes that there exist three Nash equilibria that fully capture the optimal behavior of two firms in a duopoly.

The work by Cummings et al. (2019) extend this model by directly incorporating the government as a player in the game. The work addresses how the U.S. government can ensure the cost-effective procurement of pediatric vaccinations to all U.S. children who acquire their vaccines through publicly funded health insurance (Cummings et al., 2019). The study concludes that vaccine products with higher differentiability segment markets in a positive way. Moreover, markets are at lower risk when high capacity manufacturers have moderate target profits. The study also considers scenarios in which CDC may be able to prevent monopolies through financial incentives to manufacturers.

As Cummings et al. (2019) observe the vaccine market strictly within the U.S., this paper extends the model to international markets in which different countries operate through one procurement agent, namely PAHO. The model observes the dynamics of vaccine pricing between a low income country and a high income country from the procurer's perspective. The insights drawn from this study will provide agencies such as PAHO with better knowledge in pricing trends, used to maximize cost-efficiency for its member countries. Consequently, it may contribute to increasing vaccine accessibility for low income countries.

Chapter 3

The Price Negotiation Problem

This chapter presents the optimization problem in more depth. Section 3.1 first introduces the extended parameters and variables from Cummings et al. (2019). Using these parameters and variables, Section 3.2 presents the optimization model for the public sector with its objective function subject to various constraints.

3.1 Variables and Parameters

The variables and parameters presented in this section are based on the work of Cummings et al. (2019), with modifications to account for the two-economy framework.

Both manufacturers $m \in M$ produce vaccines for both a high income country and a low income country, $i \in I$, in which each country has a public sector and a private sector. p^s_{mi} and q^s_{mi} represent the prices charged and quantities produced by manufacturer m for each sector s in country $i \in I$. As the model is formed from PAHO's perspective to optimize the prices and quantities in the public sectors of a high-income country and a low-income country, the public prices p^{pub}_{mi} and quantities q^{pub}_{mi} are treated as a variable, while the private prices p^{priv}_{mi} and quantities q^{priv}_{mi} are treated as parameters that will be determined later from the given data. z is the absolute difference in two prices charged for each public sector in country $i \in I$. Along with the parameter μ in $[0, 1]$, z weighs solutions that have a smaller absolute price difference, as shown in the objective function. The parameter $\mu \in [0, 1]$ weighs the optimal solutions that have a smaller z to be more important.

Then, we have a set of parameters required for the model. γ represents the product similarity for two products, in which 0 means the two brands are completely different and 1 means the two are completely identical. Some of the factors that determine the product similarity constant include associated histories of medically adverse events, side effects, existence of alternatives, availability and brand loyalty. Note that previous models call it the product differentiation.

D_i is the total demand of the vaccine from both public and private sectors in country $i \in I$. Furthermore, we assume that each sector operates under a linear direct demand curve as will be shown in constraint (4) of the optimization model. a_i^s, b_i, c_i are the demand curve coefficients for the linear direct demand curve in each sector $s \in S$ in country $i\ inI$.

P_m is the minimum profit threshold for each manufacturer m in M to ensure that the company can stay in business after considering its research and development (R&D) costs. The production costs are negligible in determining the minimum target profit as the initial R&D costs for the vaccine significantly outweigh the production costs. (Cummings et al., 2019). K_m is the total production capacity for each manufacturer $m \in M$. Then, the parameter U_i is the lower bounds for the private sector capacity in country $i \in I$. A threshold for the minimum quantities in the private sectors is needed in order for the price dynamics between two sectors to hold. It will be further explained in discussion of the constraint (7) of the optimization model. Lastly, G_i is the national GDP for each country $i \in I$. This constant is used to normalize the price difference in the public sector, z, as shown in constraint (1). x_i is the percentage of vaccines administered in the public sector of country $i \in I$, normalized in the range of [0,1] by dividing by 100. Conversely, $1 - x_i$ entails the proportion of vaccines administered in the private sector.

Refer to Table 3.1 for the summary of the relevant set, variables, and parameters for the model.

Table 3.1 Parameters and variables

Name	Type	Meaning
M	set	manufacturers {m,n}
S	set	sectors {public, private}
I	set	buyer country based on income level {high,low}
p^s_{mi}	variable	prices charged by $m \in M$ for sector $s \in S$ in I
q^s_{mi}	variable	quantities produced $m \in M$ for sector $s \in S$ in I
z	variable	difference between two prices for public sector in $i \in I$
γ	parameter	product similarity
D_i	parameter	total demand for country $i \in I$
a^s_i, b_i, c_i	parameters	demand curve coefficients for $s \in S$ in I
μ	parameter	objective function weight
P_m	parameter	minimum profit threshold for $m \in M$
K_m	parameter	total production capacity in $m \in M$
U_i	parameter	private sector capacity lower bound for surplus for $i \in I$
G_i	parameter	national GDP for $i \in I$
x_i	parameter	percentage of vaccination fulfilled in public sector in i in I normalized to [0,1]

3.2 Optimization Model

Using the parameters and variables above, we extend the optimization model of Cummings et al. (2019) as follows:

$$\text{objective function: minimize } \mu\Big(\sum_{m\in M, i\in I} q_{mi}^{pub} \cdot p_{mi}^{pub}\Big) + (1-\mu)z \tag{1}$$

$$\text{subject to} \qquad z \geq \frac{p_{mi}^{pub} - p_{ni}^{pub}}{G_i} \qquad i \in I, m, n \in M, m \neq n \tag{2}$$

$$\sum_{m\in M} q_{mi}^{pub} \geq x_i D_i \qquad i \in I \tag{3}$$

$$q_{mi}^{pub} + bp_{mi}^{pub} - cp_{ni}^{pub} = a_i^{pub} \qquad m, n \in M, m \neq n, i \in I \tag{4}$$

$$\sum_{s\in S, i\in I} q_{mi}^{s} \cdot p_{mi}^{s} \geq P_m \qquad m \in M \tag{5}$$

$$\sum_{s\in S, i\in I} q_{mi}^{s} \leq K_m \qquad m \in M \tag{6}$$

$$K_m - \sum_{i\in I} q_{mi}^{pub} \geq U_i \qquad m \in M, i \in I \tag{7}$$

The objective of this model is to minimize the total cost for both public sectors in two countries. The total cost is given by the quantities sold in two public sectors multiplied by the price in the public sectors. Because the observed public sector prices tend to be not too different between the manufacturers, a realistic solution would return two public sector prices to be as similar as possible (Cummings et al., 2019). The objective function given by constraint (1) achieves this goal by using the weighting parameter μ. As shown in constraint (2), the price difference in the two public sectors is divided by the national GDP in order to balance the income disparity in two different countries. When μ is sufficiently large, within the range of $(0, 1)$, the objective function returns a solution that prioritizes a small absolute price difference.

The total vaccine quantity for the public sectors is obtained by multiplying the proportion of vaccinations administered in public sector x_i by the total demand D_i. All children in the country should receive the required dosage of any particular vaccine. Hence, the total quantity of vaccines produced for the public sector should be at least as large as $x_i D_i$. However, we let $x_i D_i$ be the lower bound of the total quantity for public sectors in order to ensure the prevention of vaccine shortages (Cummings et al., 2019). It additionally provides some model flexibility for the demand estimation method described in later sections. This constraint is shown in constraint (3).

As mentioned earlier, we assume each sector operates under a linear direct demand curve given by:

$$q^s_{mi} = a^s_i - b_i p^s_{mi} + c_i p^s_{ni} \qquad m, n \in M, m \neq n, s \in S, i \in I \tag{8}$$

where a^s_i is the demand coefficient when the vaccines are hypothetically free and $c_i p^s_{ni}$ is the demand coefficient dependent on the competitor's price. This linear direct demand curve works as a constraint for the public sector as stated in constraint (4).

For a given manufacturer, its overall profit is determined by both public and private sectors of a country. We assume that PAHO wants to ensure that manufacturers make enough profit to stay in business and thereby prevent a monopoly. constraint (5) lets the manufacturers to at least meet the the minimum profit threshold. Furthermore, constraint (6) entails that, for a given manufacturer, the total quantities produced for both sectors in both countries cannot exceed its production capacity.

Lastly, constraint (7) forces the remaining vaccines after selling in the public sectors of both countries to exceed the minimum threshold needed for the private sector prices and quantities to be determined by the Bertrand-Edgeworth-Chamberlin equilibrium. In other words, the quantities reserved for the two public sectors define the quantities that will be allocated to the private sector. In the private sector, the manufacturers compete independently of PAHO.

For the private sector equilibrium parameters, we use the values derived by Behzad and Jacobson (2016) and Cummings et al. (2019):

$$U_i = \frac{a_i^{priv}(1+\gamma)}{\gamma} \cdot \left(1 - \frac{2(1-\gamma)^{0.5}}{(1+\gamma^{0.5})(2-\gamma)}\right) \qquad i \in I \tag{9}$$

$$p_{mi}^{priv} = \frac{a_i^{priv}}{2b_i - c_i} \qquad m \in M, i \in I \tag{10}$$

$$q_{mi}^{priv} = b_i \cdot p_{mi}^{priv} \qquad m \in M, i \in I \tag{11}$$

$$b_i = \frac{1}{(1+\gamma)(1-\gamma)} \qquad i \in I \tag{12}$$

$$c_i = \frac{\gamma}{(1+\gamma)(1-\gamma)} = \gamma \cdot b_i \qquad i \in I \tag{13}$$

and a_i^{priv} is determined from publicly available price and demand data for each country, as described in the next section.

Chapter 4

Case Study of DTaP

In order to validate the optimization model from Chapter 3, we apply the model to a case study. Section 4.1 discusses the selection of appropriate countries for the model. Section 4.2 provides background information on DTaP, the selected vaccine for the case study. It also includes necessary assumptions made for the model. Section 4.3 explains the process of parameter estimation for both countries. Thereby, we set up the appropriate conditions for the optimization model to be solved through mathematical programming.

4.1 Selection of Appropriate Countries

We use the U.S. as a high income country case as this model is an extension of Cummings et al. (2019)'s work, modelled for the U.S. pediatric market. For the low income country case, Paraguay is selected. There are several reasons for the selection: first, because we are observing the dynamics of a pricing model within the PAHO framework, the two countries need be members of PAHO. Although the U.S. has its own monopsonistic agent to procure vaccines (namely the Center for Disease and Control), the country remains a member of PAHO. For the case study, it is assumed that the U.S. procures DTaP through PAHO. Secondly, it is necessary to have some level of GDP disparity between two countries. Lastly, because the model incorporates both the public sector and private sector in each country, a country with a substantial presence of the private healthcare sector is desired.

The healthcare of Paraguay consists of the public sector, the Institute of Social Security and the private sector (OECD Development Center, 2019).

Even though the Institute of Social Security is often regarded as a separate entity, in this model, it is considered as a subsystem of the public sector. Because the exact data on the distribution of healthcare service utilization is not available, we utilize the coverage estimations from Kieninger et al. (2015). The coverage by each sector is estimated based on the *2008 Continuous Household Survey*, conducted by Department of Vaccines and Biological Products of WHO. The results state that, 54.7% of the respondents received outpatient treatment from the public sector; 13.8% from Institute or Social Security; and lastly, 31.5% from the private sector, which includes pharmacies and others (Kieninger et al., 2015). Since we consider the Institute of Social Security as a subsystem of the public sector, we assume 68.5% for the percentage of vaccine administered in the public sector and 31.5% for that of private sector. Therefore, x_i for Paraguay is 0.685.

4.2 Information on the Vaccination

As Cummings et al. (2019) consider the monovalent DTaP duopoly in the U.S., we select DTaP as the vaccine for our model. DTP refers to any medication that vaccinates against diphtheria toxoid (D), tetanus toxoid (T), and acellular pertussis (P). For DTP, there are two main types of vaccines: the first is DTwP that contains a whole cell for the the pertussis component. Then, there is DTaP that contains an acellular component for pertussis (Holt et al., 2016). While some form of DTP vaccination for infants is required in most countries, the preference of DTaP or DTwP varies depending on the country and its national immunization program.

The U.S. is one of the many countries that includes DTaP in its pediatric immunization schedule. In particular, the Vaccines for Children (VFC) is a federal program through the CDC that was established in 1994 to provide vaccines at no cost for eligible children from birth (Cummings et al., 2019). The VFC covers a wide range of vaccinations that includes the 5-dose DTaP. The CDC recommends DTap to all children at 2, 4, and 6 months, with boosters at 15 through 18 months, and at 4 through 6 years (Centers for Disease Control and Prevention, 2019). In the current U.S. market, there exists a duopoly for DTaP vaccine: Infanrix produced by GlaxoSmithKline and Daptacel produced by Sanofi Pasteur.

On the other hand, in many Latin American countries, DTwP is the most preferred form of DTP vaccination. Paraguay implemented The Expanded Program on Immunization (EPI), managed by the Ministry of Public Health and Social Welfare of Paraguay, with its goal of making vaccinations available to all children. This program follows the standard vaccination schedule from PAHO/WHO and requires 2-dose DTwP for all infants, with the first dose at 18 months of age, and the second booster at 4 years of age (Ministerio de Salud Publica Y Bienestar Social, 2019).

In regards to the model, there are some necessary assumptions to be made. While the model stipulates a duopoly for monovalent vaccine in the international market, the U.S. uses DTaP and Paraguay uses DTwP. As we cannot compare two different types of monovalent vaccines in the model, the duopoly of DTaP between Infanrix and Daptacel is also assumed in Paraguay. As a consequence of this assumption, the model may not accurately reflect the market conditions in Paraguay. However, this assumption allows us to observe the pricing dynamics of the same products in a low income country and a high income country, achieving the goal of gaining insights on vaccine procurement in a two-economy duopoly.

4.3 Estimation of Parameters

This section presents our estimates for the model parameters. For the case of the U.S. market parameters, we use the same values as in Cummings et al. (2019). We estimate the Paraguay market parameters using the same approach as Cummings et al. (2019).

4.3.1 Estimation of Total Demand

Cummings et al. (2019) estimate the total annual demand for DTaP in the U.S. market as the product of the number of annual births and the expected number of DTaP doses per child. They report a 2018 estimated demand of 4.34M doses, which we use here for the U.S. market.

Using a similar method from Section 4.3.1, we now estimate the total annual demand for Paraguay. WHO/UNICEF annually publishes the national vaccination coverage estimations, assuming the 3-dose DTP vaccination. Paraguay's annual DTP coverage (%) is acquired from this source (World Health Organization, 2018). Since the data provide the estimates of only the first dose coverage (DT1) and the third dose coverage (DT3), the second dose coverage (DT2) is estimated to be the midpoint of DT1 and DT3. Table 4.1 presents the annual national coverage as well as the annual number of births in Paraguay. Then, each coverage is multiplied by the annual birth cohort to obtain the total number of doses administered for each D1,D2,

Table 4.1 Annual DTP Coverage (%) and Number of Births in Paraguay

Year	DT1 (%)*	DT2 (%)*	DT3 (%)*	Birth**
2010	95	93	91	1.419×10^5
2011	95	93.5	92	1.418×10^5
2012	94	92.5	91	1.416×10^5
2013	97	94	91	1.415×10^5
2014	95	94	93	1.421×10^5
2015	96	94	92	1.426×10^5
2016	94	93	92	1.432×10^5
2017	95	93	91	1.437×10^5

*The annual DTP Coverage is obtained from World Health Organization (2018).
** The annual number of births in Paraguay is obtained from the UN (2019).

D3. Lastly, the sum of number of DT1, DT2, DT3 administered in one year yields the total number of DTP dosage. This is shown in Table 4.2. Note that WHO/UNICEF uses different methods to estimate the national coverage, compared to the CDC, yielding a higher expected dose per child compared to that of the U.S.

Finally, Table 4.3 presents the total annual demand for Paraguay. Recall from Section 4.1 that we assume the public sector of Paraguay fulfills around 68.5% of the total demand. The public sector demand was estimated by multiplying the total demand by 68.5%. The rest is allocated to the private sector.

Table 4.2 Annual Number of DTP Doses Administered

Year	DT1	DT2	DT3	Total Dose
2010	1.348×10^5	1.320×10^5	1.292×10^5	3.960×10^5
2011	1.347×10^5	1.326×10^5	1.304×10^5	3.977×10^5
2012	1.331×10^5	1.310×10^5	1.289×10^5	3.931×10^5
2013	1.372×10^5	1.330×10^5	1.287×10^5	3.989×10^5
2014	1.350×10^5	1.335×10^5	1.321×10^5	4.006×10^5
2015	1.369×10^5	1.341×10^5	1.312×10^5	4.022×10^5
2016	1.346×10^5	1.331×10^5	1.317×10^5	3.994×10^5
2017	1.365×10^5	1.336×10^5	1.307×10^5	4.008×10^5

Table 4.3 Total Demand Estimates for Paraguay

Year	Total demand	Public sector (68.5%)	Private sector (31.5%)
2010	3.960×10^5	2.712×10^5	1.247×10^5
2011	3.977×10^5	2.724×10^5	1.253×10^5
2012	3.931×10^5	2.693×10^5	1.238×10^5
2013	3.989×10^5	2.733×10^5	1.257×10^5
2014	4.006×10^5	2.755×10^5	1.258×10^5
2015	4.022×10^5	2.755×10^5	1.267×10^5
2016	3.994×10^5	2.736×10^5	1.262×10^5
2017	4.008×10^5	2.745×10^5	1.262×10^5

4.3.2 Estimation of the Objective Function Weight

Recall from Chapter 3 that the objective function is defined as:

$$\text{objective function: minimize } \mu\Big(\sum_{m\in M, i\in I} q_{mi}^{pub} \cdot p_{mi}^{pub}\Big) + (1-\mu)z \tag{1}$$

It contains the weight function μ to prioritize a solution with a smaller manufacturer price difference. Cummings et al. (2019) obtained $\mu = 10^{-4}$ through an empirical process, considering the order of magnitude for the cost outputs. This value of μ reasonably prioritizes minimizing the government costs while also finding the optimal solution that has a small price difference z (Cummings et al., 2019).

4.3.3 Estimation of Linear Demand Coefficients

From Cummings et al. (2019), we obtain a formula to estimate the DTaP demand curve intercepts a_i^s from the vaccine price data. Let q_{miy}^s and p_{miy}^s be the quantity and price from sector $s \in S$ in country $i \in I$, produced by manufacturer $m \in M$, during the year $y \in 1, ..., Y$. Then, the estimate of a_i^s is given by the average of a_{iy}^s for year 1 through Y:

$$a_i^s = \frac{1}{Y}\sum_{y=1}^{Y}\left(\frac{1}{2}\sum_{m\in M, i\in I} q_{miy}^s + \frac{10^5}{2+2\gamma}\sum_{m\in M, i\in I} p_{miy}^s\right) \quad s \in S$$

Using these equations, Cumming et al. (2019) approximate the linear demand coefficient a_i^s of the U.S. to be:

$$a_{US}^{pub} = \left(1.365 + \frac{1.553}{1+\gamma}\right) \times 10^6$$

$$a_{US}^{priv} = \left(1.030 + \frac{2.389}{1+\gamma}\right) \times 10^6$$

Note that for the U.S., the equations are scaled by 10^6 as vaccine quantities are in the magnitude of 10^6 while the prices are in the magnitude of 10^1. As a reference, the U.S. prices of Infanrix and Daptacel are obtained from Cummings et al. (2019) and are shown in Table 4.4.

Similarly, using the same method, the demand intercepts a_i^s for Paraguay are computed. In regards to the public sector price, PAHO annually publishes

Table 4.4 Annual Infanrix and Daptacel Prices in the U.S*

U.S.	**Public Sector**		**Private Sector**	
Year	Inf	Dap	Inf	Dap
2010	$13.75	$13.75	$21.20	$23.75
2011	$14.51	$13.25	$21.20	$24.40
2012	$15.35	$15.00	$21.20	$25.29
2013	$15.76	$15.38	$21.20	$25.98
2014	$15.76	$15.38	$21.20	$25.98
2015	$16.15	$16.04	$21.20	$27.17
2016	$16.85	$16.73	$22.40	$28.41
2017	$17.73	$17.16	$22.40	$29.20

*The annual prices for Infanrix and Daptacel in each sector of the U.S. are obtained from Cummings et al. (2019).

the weighted averages of the contract prices for DTaP; however, it does not disclose the names or the number of the selected manufacturers. The weighted averages of the annual DTaP contract prices are shown in Table 4.5. Note that the price for 2010 is an estimate from the 2011 price as PAHO started to publish the prices in 2011. On the other hand, in regards to the demand intercept for private sector of Paraguay, there were limitations in obtaining the exact annual vaccine prices. Thus, as an alternative, the average price difference (%) between the two sectors in the U.S. was applied to extrapolate the private sector prices in Paraguay. From calculations, the average price of DTaP in the private sector of the U.S was 65.04% more expensive than that of public sector of the U.S. Thus, we assume the average vaccine price in the private sector of Paraguay to be \$18.39, compared to \$11.14 in the public sector. Using these values, the intercepts for Paraguay are estimated and shown in the equations down below:

$$a_{Par}^{pub} = \left(1.365 + \frac{1.114}{1+\gamma}\right) \times 10^5$$

$$a_{Par}^{priv} = \left(0.628 + \frac{1.839}{1+\gamma}\right) \times 10^5$$

Similar to the previous linear demand coefficients, the equations for Paraguay are scaled by 10^5 as vaccine quantities are in the magnitude of 10^5 while the prices are in the magnitude of 10^1.

4.3.4 Estimation of Product Similarity

Recall from Chapter 3 that γ represents the product similarity for Infanrix and Daptacel, in which 0 means the two brands are completely different and 1 means the two brands are completely identical. Some of the factors that determine product similarity are associated histories of medically adverse events, side effects, existence of alternatives, availability and brand loyalty. Since some of these factors are not quantifiable, a sensitivity analysis is conducted on the range of product similarity γ. While using $\gamma = 0.25$ as a default value, we extend the range to (0,0.5) in the analysis, following the method from Cummings et al. (2019). This is based on the assumption that healthcare providers can select between syringe, single-dose vial and multi-dose vials (Cummings et al., 2019).

Table 4.5 DTaP Contract Prices for PAHO**

Year	**Price**
2010	$10.00*
2011	$10.00
2012	$10.50
2013	$10.80
2014	$8.00
2015	$12.00
2016	$12.80
2017	$15.00

* The price in 2010 is an estimate from the price in 2011.
** The annual contracted prices of Infanrix and Daptacel through 2011-2017 are obtained from PAHO (2018).

4.3.5 Estimation of Total Production Capacity

In this model, we assume symmetric production capacity for both manufacturers. In other words, GlaxoSmithKline and Sanofi Pasteur, have the same amount of production capacity for Infanrix and Daptacel, respectively. However, since the total production capacity is not publicly available, we let the sum of total demand for the U.S. and Paraguay be the production capacity as it is expected that a manufacturer does not produce more than the total market demand (Cummings et al., 2019).

4.3.6 Estimation of Target Profit

We assume that PAHO ensures a satisfactory profit for each manufacturer to stay in business, to avoid monopoly in the market. Cummings et al. (2019) use the previous year's demand and prices as the target profit for the following year :

$$P_{m,y} = \frac{D_{y-1}}{2} \cdot \left(x_i p^{pub}_{m,y-1} + (1 - x_i) p^{priv}_{m,y-1} \right) \qquad m \in M$$

Cummings et al. (2019) obtained the profit in 2018 from the U.S. market to be \$39.8M for GlaxoSmithKline and \$45.1M for Sanofi Pasteur. Using the same approach, we estimate the target profit in the Paraguayan market to be \$0.39M for GlaxoSmithKline and \$0.34M for Sanofi Pasteur. Since P_m for a given manufacturer $m \in M$ is the sum of profits made from both U.S. and Paraguay, we obtain the target profit in 2018 for GlaxoSmithKline to be \$40.2M and \$45.4M for Sanofi Pasteur. As in Cummings et al. (2019), we can validate that these are reasonable target profits by comparing these values to each manufacturer's estimated R&D expenses. Cummings et al. (2019) estimates the R&D costs to be \$33.4M and \$43.1M for GlaxoSmithKline and Sanofi Pasteur respectively. Thus, because our target profit values are greater than the R&D costs, this serves as a validation that the target profit values are reasonable.

4.3.7 Estimation of Private Sector Capacity Lower Bound

Finally, this section discusses the private sector parameter U_i, which is needed to assume BC equilibrium. We use the equation that Cummings et al. (2019) provide:

$$U_i = \left(\frac{a_i^{priv}(1+\gamma)}{\gamma}\right) \cdot \left(1 - \frac{2(1-\gamma)^{1/2}}{(1+\gamma)^{1/2}(2-\gamma)}\right) \quad i \in I$$

This concludes the estimations of the parameters. The summary is presented in Table 4.6.

Table 4.6 Summarized Parameter Values

Model Component	**U.S.**	**Paraguay**
D_i	4.34M*	0.39M***
x_i	0.57*	0.685****
a_i^{pub}	$\left(1.365 + \frac{1.553}{1+\gamma}\right) \times 10^{6*}$	$\left(1.365 + \frac{1.114}{1+\gamma}\right) \times 10^5$
a_i^{priv}	$\left(1.030 + \frac{2.389}{1+\gamma}\right) \times 10^{6*}$	$\left(0.628 + \frac{1.839}{1+\gamma}\right) \times 10^5$
μ*	10^{-4}	10^{-4}
γ*	(0, 0.5)	(0, 0.5)
K_{inf}, K_{dap}**	4.42M	4.42M
P_{inf}, P_{dap}**	\$40.2M, \$45.4M	\$40.2M, \$45.4M

* The parameter estimates for the U.S. come from Cummings et al. (2019).
** The production capacity and target profit have been adjusted to fit the two-economy model, using the methods from Cummings et al. (2019).
*** The demand estimate for Paraguay is obtained from the UN (2019).
**** x_i for Paraguay is obtained from Kieninger et al. (2015).

Chapter 5

Results

The goal of this analysis is to gain insights on the vaccine pricing dynamics in a two-economy duopoly, that will inform pricing strategy for agencies such as PAHO who negotiate vaccine prices on behalf of many countries. Section 5.1 describes the mathematical programming from which the solutions are obtained. Section 5.2 discusses the empirical results.

5.1 Mathematical Programming

The Network Enabled Opimization System (NEOS) server is a free internet-based service for numerical optimization problems, providing access to more than 60 types of solvers (Wisconsin Institute for Discovery at the University of Wisconsin in Madison, 2019). Among those solvers, the Branch-And-Reduce Optimization Navigator (BARON) solves purely continuous, purely integer, and mixed integer nonlinear problems (NEOS Servor, 2019). The optimization model and the necessary case study data were formulated in A Mathematical Programming Language (AMPL) and were submitted to BARON to obtain solutions.

5.2 Solutions for the Model

Cross subsidization is a pricing strategy to subsidize a product from the profits of other products, usually within a firm or a manufacturer. This strategy allows the manufacturer to offer a lower pricing point for the targeted consumer segment. In the context of the case study from Chapter 4, the concept of cross subsidization can be applied to PAHO's vaccine

Table 5.1 The Price and Quantity Output for the Public Sectors of the U.S. and Paraguay

$\gamma = 0.25$		**US**	**Paraguay**
Infanrix	Price	\$4.53	\$11.64
	Quantity	2.368M	0.13M
	Net Cost	\$10.73M	\$1.54M
Daptacel	Price	\$9.14	\$11.63
	Quantity	1.75M	0.13M
	Net Cost	\$16.03M	\$1.54M
Total PAHO Cost		\$26.76M	\$3.08M

procurement process by lowering the total cost of DTaP vaccines for the low income country (Paraguay), sustained by a higher total cost for the high income country (US). In this case, the cross subsidization is rather indirect, and is possible due to the large amount of vaccines that PAHO must purchase to meet the U.S. demand.

With the default value of product similarity at $\gamma = 0.25$, the optimal pricing solution is presented in the Table 5.1. It compares the DTaP price and quantity allocation between the two countries. The net cost is obtained by multiplying its price and quantity.

Recall from Chapter 3 that the objective function of the model is to minimize the total PAHO cost while meeting all the constraints. Thus, the values obtained are the costs of vaccines only applicable to the public sector, given the parameter inputs. In order to validate this model, we compare the price output with the actual prices of DTaP vaccines in 2018.

The true contracted prices of Infanrix and Daptacel in the U.S. public sector are \$18.19 and \$17.61 respectively (Cummings et al., 2019). For the price in Paraguay, the weighted average cost of the pediatric DTaP is \$15.00 (PAHO, 2018). From this weighted average, we estimate the Paraguay's public sector prices for each vaccine using the price difference percentage in the U.S. The calculated prices of Infanrix and Daptacel in Paraguay are

$15.18 and $14.81 respectively. The direct comparison for the prices are shown in Figure 5.1.

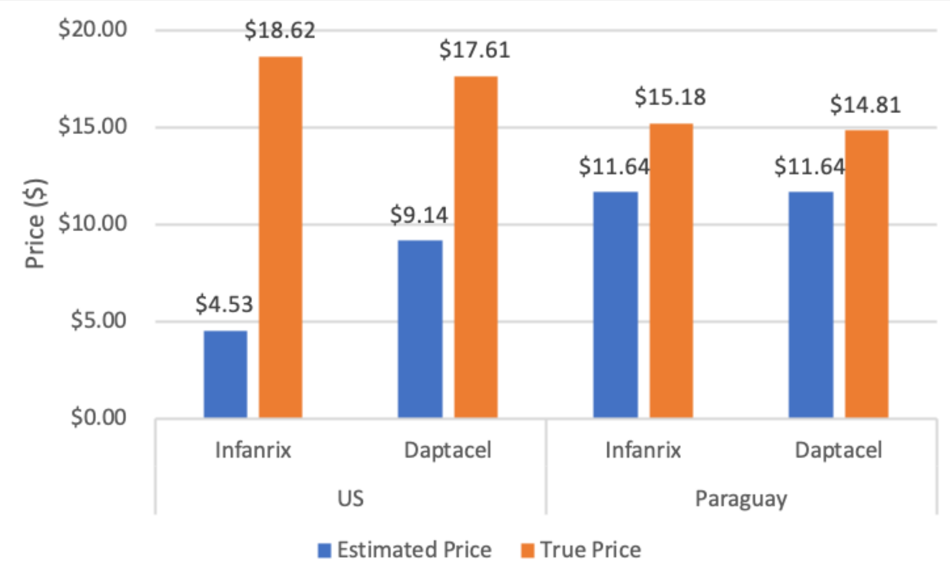

Figure 5.1 Comparison of Estimated Price and True Price for DTaP

Recall that a sensitivity analysis was conducted on few selected product similarity values. Figure 5.2 presents the results of predicted prices in the U.S. market. The range of Infanrix price is from $3.79 to $17.87, while the range of Daptacel price is from $5.55 to $10.48. As we can see, the price generally increases as product similarity increases. This is an unexpected result that does not accurately capture the market since, in most cases, a manufacturer would have to decrease the price as its product is more similar to the competing products in the market. A sensitivity analysis on few selected product similarity values in the Paraguayan market shows a similar result as that of the U.S. market.

The predicted prices are lower than the actual contracted prices. However, this is somewhat an expected outcome as the previous models from Cummings et al. (2019) and Behzad and Jacobson (2016) also had output prices lower than the actual prices. For example, in the model from Cummings et al. (2019), the predicted prices for Infanrix and Daptacel in the public sector of the U.S. were $18.62 and $8.45 respectively. Cummings et al. (2019) attribute one of the factors for the lower approximation to be the model's characterization of the government. Similarly, in this model,

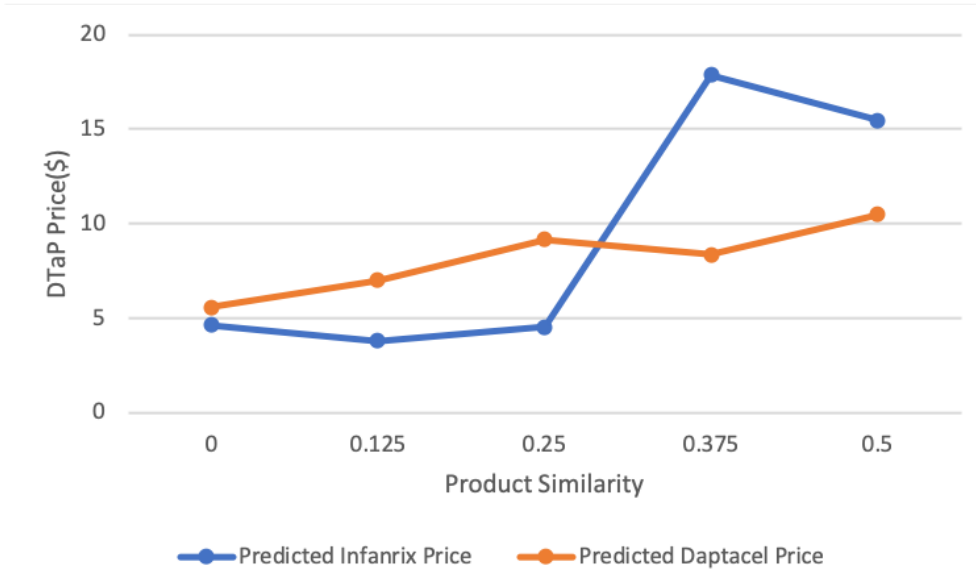

Figure 5.2 Range of the Predicted DTaP Price in the U.S.

PAHO is the central institution that the optimization is solved for, with the only specified objective being minimizing the net cost. Because PAHO is a complex institution, serving beyond the two countries, there may be other objectives of PAHO that contributes in higher contract prices. Furthermore, lack of *tacit collusion* assumption is another factor that Cummings et al. (2019) suspects. It refers to the pricing strategy in which firms seek higher profits than Bertrand behavior permits by setting higher prices until a competing firm lowers its price (Robbins et al., 2013). Lastly, the DTaP prices in Paraguay are estimates using the U.S. price difference of two products' prices - where the market characteristics differ vastly from that of Paraguay's vaccine market. This assumption may have contributed in the underestimation of the prices.

While the general underestimation of the prices was expected and explained in the previous paragraph, the substantial difference in the DTaP vaccine prices between the U.S. and Paraguay is an unforeseen result. As shown in Table 5.1, Infanrix is predicted to cost \$4.53 in the U.S. and \$11.64 in Paraguay. Similarly, Daptacel is predicted to cost \$9.14 and \$11.63 in Paraguay. This is the opposite of the desired cross-subsidization effect. This result may be attributed to a possible flaw in the model, specifically in the objective function. Because the objective function minimizes total public sector cost, and since the volume of the U.S. market is so large, it may

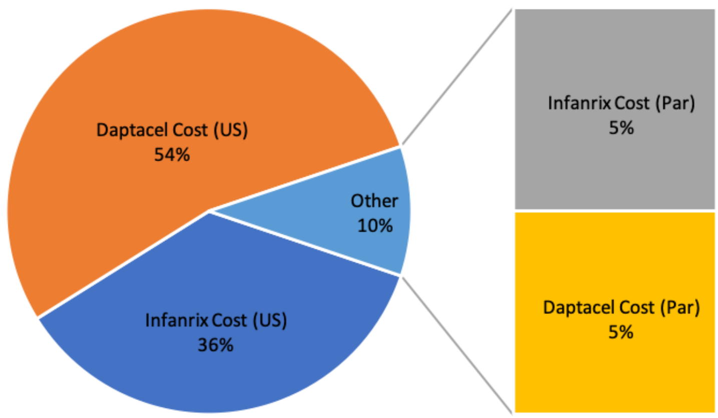

Figure 5.3 PAHO Total Spending Segmented (%)

have returned a solution that prioritizes lowering the prices in the U.S. The proportion of the U.S. market in total PAHO spending is shown in Figure 5.3 to emphasize the volume of the U.S. market. Considering that PAHO's net spending is around $30M, 90% of the net cost is spent on purchasing DTaP vaccines for the U.S. This matter is further discussed in Conclusion.

While considering the possible flaw in the model, the output results for the U.S. market imply that it benefited through PAHO's vaccine procurement compared to the independent vaccine procurement through CDC. The direct comparison is shown in Figure 5.4. The predicted DTaP prices from the PAHO model were lower than the predicted DTaP prices from the U.S.-only model in Cummings et al. (2019). While Daptacel procured by CDC is slightly cheaper ($8.45) than Daptacel procured by PAHO ($9.14), the price difference in Infanrix is much larger. The predicted Infanrix price procured by CDC is $18.62 and the same product procured by PAHO is $4.53 (Cummings et al., 2019). This analysis for Paraguay is omitted as we do not have a Paraguay-only model for comparison.

While PAHO's vaccine procurement provided the U.S. market with a lower price, we must consider the possible flaw discussed in the previous paragraph. Again, this result may be attributed the flaw in the objective function, as it may have prioritized returning a lower cost in the large market at the expense of higher costs in the small market.

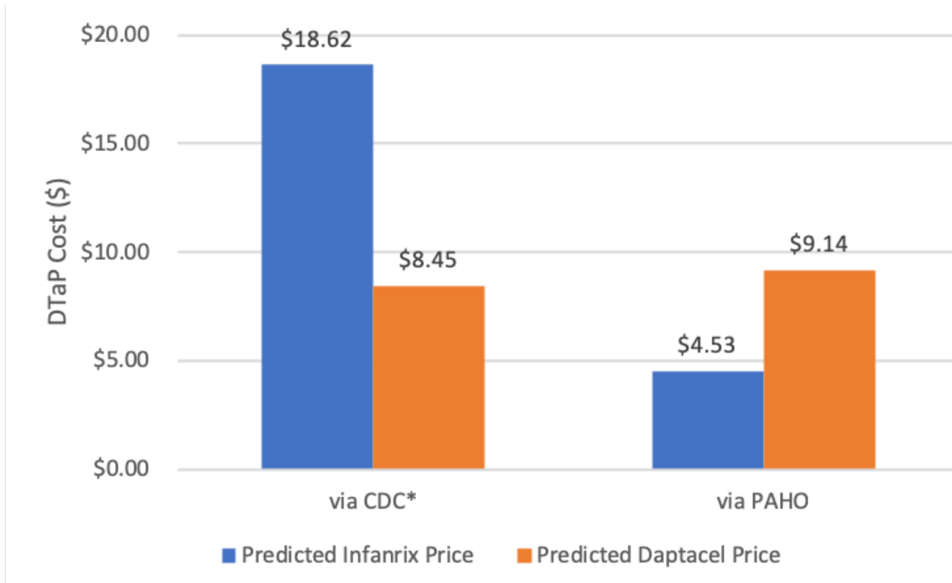

Figure 5.4 DTaP Price Comparison by Procurement Agent
*The predicted Infanrix and Daptacel costs procured through CDC is from Cummings et al. (2019).

To conclude, the output of the model presented some unexpected results. For example, the cross-subsidization occurred in the opposite direction, from Paraguay to the U.S. While this is an undesirable result, it still validates idea that some form of cross-subsidization occurs in PAHO vaccine procurement. When the direction of the cross-subsidization is reversed, from a high income country to a low income country, it could contribute in providing a lower price for the low income country, ultimately improving the vaccine accessibility.

Chapter 6

Conclusion

In this work, we presented an optimization problem to observe the vaccine pricing dynamics in a two-economy duopoly from the perspective of a centralized procurement agency, such as PAHO. The objectives of the model are : (1) minimizing the total government cost (2) ensuring a satisfactory profit for all manufacturers (3) meeting all demands from both countries. The model is a direct extension of the existing work of Cummings et al. (2019) that models one-economy duopoly in the U.S.

We formulated a case study in order to validate the model. The model was applied to the DTaP duopoly in the U.S. and Paraguay, procured by PAHO. The results of the case study provided some interesting insights for the pricing dynamics in two countries. The inversely proportional relationship of price and quantity is well-known and highly applicable to many real cases. The relationship still holds for PAHO's vaccine procurement mechanism, as PAHO is responsible for purchasing a large sum of vaccines to meet all demands from member countries. With the decreased prices following the inverse relationship, we incorporated the idea of cross-subsidization within PAHO. However, it is important to acknowledge that there exists a possible flaw in the model as the output prices presented a significantly cheaper price for Infanrix in the U.S. than that of Infanrix in Paraguay. This is the opposite of the desired result as the cross-subsidization occurred in favor of the high income country. While considering this flaw, the model output was directly compared with one-economy model results. The comparison implied that the U.S. market benefits from a cheaper price through PAHO's vaccine procurement. Thus, in order for PAHO to purchase vaccines at the lowest price possible and initiate the subsidization process, it is of best interests for PAHO to maintain countries with high demand as members.

Moreover, it has been shown that some form of cross-subsidization does occur in PAHO vaccine procurement. When the cross-subsidization occurs in the desired direction, from a high income country to a low income country, it could contribute in improving the vaccine accessibility for a low income country.

One of the limitations of this work is that the public/private sector healthcare system observed in the U.S. is relatively rare in the countries served by PAHO. As such, the U.S./Paraguay comparison used here is not a perfect analogy for the sorts of negotiations that PAHO would use. Thus, a potential work could include extending the model to have more flexibility in the healthcare structure of the selected countries or the type of vaccines. As Cummings et al. (2019) writes, this model separates a huge market into one antigen. In reality, the pediatric vaccine market is layered with many intertwined relationships between different types of vaccines and manufacturers. Future work could incorporate this matter in an attempt to more accurately capture the vaccine market.

Recall that the predicted DTaP prices from the model were substantially less than the true contracted price. We suspect flaws in some of the parameter estimation methods. For instance, the price difference (%) between the public sector and private sector of the U.S. was used to calculate the parameters of Paraguay. More careful execution of formulating these assumptions may positively affect obtaining an accurate portrayal of the pricing dynamics. Moreover, a revision in the objective function should be considered in order to investigate the ironic results of cross-subsidization. For example, the public sector costs can be weighted by the inverse GDP of each country in the objective function.

Another potential future work using this model could investigate a unique duopoly of a monovalent HPV vaccine in the global pharmaceutical market, namely Cervarix and Gardasil. As the awareness for HPV vaccination is growing exponentially across the globe, it may be beneficial to study the HPV vaccine procurement through PAHO or other public health organizations. Maintaining the two-economy model between a high income country and a low income country could be used to also incorporate important cultural contexts that are often overlooked in research.

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