A MULTI-ATTRIBUTE APPROACH FOR SETTING PEDIATRIC VACCINE STOCKPILE LEVELS

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ABSTRACT. Routine immunization is the most effective public health strategy to prevent the occurrence and spread of infectious diseases. An important factor impacting such effectiveness is the availability of a stable vaccine supply. Vaccine supply interruptions are likely and can prevent children from receiving a full course of vaccinations and hence, increase the risk of disease outbreaks. In the United States, public health officials have established the Pediatric Vaccine Stockpile Program (PVSP) as the best strategy to mitigate the impact of vaccine supply interruptions. The PVSP aims to maintain a six-month national supply of routinely administered pediatric vaccines. When deciding how many vaccine doses to order for the next fiscal year, public health decision-makers must not only minimize the impact of potential vaccine shortages, but also, maintain or increase vaccine coverage rates while minimizing costs. This paper uses the relative importance of each pediatric vaccine to define a multi-attribute utility function that models the conflicting interests of PVSP public health decision-makers when ordering vaccines for the next fiscal year. The aim of the resulting framework is to assist decision-makers in managing the PVSP. As an illustration, this paper explores the implications of optimizing a proposed expected utility function under budget constraints for hypothetical (albeit likely) vaccine supply scenarios, and the potential behavior of public health decision-makers.

1. Introduction. In the United States, recent pediatric vaccine production interruptions have lead to supply shortages that have resulted in numerous children not being fully immunized according to the Recommended Childhood Immunization Schedule (RCIS) [5]. The risk of vaccine supply interruptions depends on several factors, such as a limited number of manufacturers in the market, lengthy and complex development and production processes, stringent government controls, low valuation of vaccines, and communication issues between federal government agencies and key stakeholders in the manufacturing industry [21, 16]

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To reduce the impact of pediatric vaccine shortages, the United States government created the Pediatric Vaccine Stockpile Program (PVSP). Since 1993, the PVSP has been required to maintain a six-month rotating vaccine stockpile, which on no less than eight occasions, has been used to ameliorate potential vaccine shortages [16, 18]. The PVSP is administered and managed by the Centers for Disease Control and Prevention (CDC).

At present, it is precarious, if not impossible, to respond to vaccine supply shortages by relying on vaccine manufacturers’ ability to rapidly increase production. Until new technological developments reduce the length of vaccine production processes and provide greater manufacturing flexibility, maintaining vaccine stockpiles will remain the most effective way to mitigate the impact of supply shortages. Jacobson et al. [13, 14] propose a stochastic model to determine stockpile levels that minimize the risk of a vaccine shortage during a vaccine supply interruption while maintaining a given immunization coverage rate. However, the CDC is not only interested in maintaining coverage rates during a vaccine shortage. Indeed, the CDC must administer vaccine stockpiles while fulfilling numerous responsibilities [9]: controlling and preventing infectious diseases; providing vaccine coverage and safety; assuring service delivery; sustaining and improving vaccination coverage rates; assuring vaccine purchases; and supporting immunization financial policies and practices. This paper proposes a framework that can be used to determine the number of new doses that must be ordered to and released from the PVSP each fiscal year such that the CDC can simultaneously fulfill its many responsibilities. In particular and without loss of generality, assume that public health decision-makers administering the PVSP must simultaneously minimize the impact of a potential vaccine shortage, maximize the coverage levels in society, and maximize cost savings.

These three objectives are conflicting in nature. For example, although larger vaccine inventories can be used to decrease the impact of vaccine shortages and increase society coverage levels, they also increase vaccine stockpile costs. Alternatively, to increase coverage levels, vaccines doses can be released from the stockpiles, which in turn increases the impact of a potential vaccine shortage in the event of a supply interruption. In addition to these tradeoffs, determining how many pediatric vaccine doses should be added or removed from the stockpiles is further complicated by the relative differences in each vaccine’s manufacturing capacity, by the current immunity levels of society against pediatric diseases, and by the relative morbidity and mortality of each pediatric disease.

Considering that each year, a budget is available to purchase vaccines for the PVSP in the next fiscal year, the proposed framework results in a multi-attribute optimization problem under budget constraints. The problem can be considered an extension of the utility maximization problem (UMP), in which a public health decision-maker must decide how to spend an allocated budget in order to maximize a utility function, subject to constraints bounding the problem decision variables.

The application of multi-attribute utility models, as well as of multi-criteria decision-making processes is rich and increasingly relevant for complex problems with multiple stakeholders. These applications range from the analysis of environmental issues [12], to the solution of lot-sizing problems in complex supply chains [19]. Applications dealing with inventory problems have mostly focused on the maintenance of spare parts [2, 22], and on determining best inventory categories rather than on stockpile levels [4]. Furthermore, the number of studies describing
the application of multi-attribute utility models that facilitate the decision-making process in supply chains of public health interest is limited.

This paper is organized as follows. Section 2 presents the vaccine ordering problem and proposes a mathematical form for its multi-attribute objective function. Section 3 decomposes this function, mathematically defines each attribute, and describes the resulting objective function. Section 4 discusses an illustrative computational example, while Section 5 provides concluding comments.

2. Utility Maximization Problem (UMP). This section describes how the vaccine ordering problem can be modeled as an application of the utility maximization problem. First, the UMP is structured for the vaccine ordering problem. Then, necessary assumptions needed to formulate the multi-attribute utility function are presented. The resulting utility function is then decomposed into a set of single-attribute utility functions.

2.1. UMP structure and assumptions. The vaccine ordering problem can be seen as an extension of the classic utility maximization problem (UMP) [17]. Given a consumption set $R^L_+$ containing $L$ types of vaccines in the PVSP, with prices $p \in R^L_+$, and an available budget $\Omega$, the goal is to maximize a multi-attribute utility function $U(Y_1, Y_2, Y_3)$, where each of the attributes $Y_1, Y_2, Y_3$ is a function of selecting the best affordable vaccine package, $x \in R^L_+$, and the number of vaccine doses, $w \in R^L_+$, to release. Therefore,

$$ (x^∗(p, \Omega), w^∗) = \arg \max_{(x \in B(p, \Omega), w)} U(Y_1(x, w), Y_2(x, w), Y_3(x, w)),$$

where

$$B(p, \Omega) \equiv \{x \in R^L_+: px \leq \Omega\}.$$

Prior to the beginning of the next fiscal year, and after the budget allocated for purchasing vaccines for the PVSP has been approved, public health decision-makers must determine the number of vaccine doses to order and the number of doses to release from the stockpiles such that at the beginning of the next fiscal year, when the ordered vaccines are included in the PVSP, the resulting stockpile levels simultaneously optimize the following attributes,

$Y_1$: the impact level of a potential vaccine shortage (in $),

$Y_2$: the coverage level of society (in %),

$Y_3$: cost savings (in $).

2.2. Utility assessment. Once the attributes of interest are determined, solving the vaccine ordering problem requires the form of the multi-attribute utility function to be established, as well as the mathematical expression of the attributes and their individual utility functions. For this purpose, this paper only considers a type of public health decision-maker that shows three clear intuitive preferences: increasing stockpiles of vaccines that are more vulnerable to supply interruptions, increasing vaccine stockpiles against diseases for which society has lower coverage, and increasing the stockpiles of vaccines for diseases that have a greater impact on society, based on the diseases’ morbidity and mortality.

Several assumptions are needed to assess the type of multi-attribute utility function to be considered. First, decision-makers are mainly concerned that the stockpile levels of the PVSP minimize the potential impact of vaccine shortages. Second, the actual impact of a vaccine shortage only depends on the backlogged demand of unvaccinated newborn children during a vaccine supply interruption. Third, increases in population coverage due to vaccination mostly occur during periods when
there are no vaccine supply interruptions. Fourth and finally, any incurred financial costs deals with replenishing a PVSP for the next fiscal year. Hence, the certain equivalent for a decision-maker facing uncertain outcomes for the impact of a vaccine shortage will not change for different values of coverage or cost. Similarly, a decision-maker facing uncertain costs for replenishing the PVSP will not change its certain equivalent for any given value of coverage and to a lesser degree to the impact of a vaccine shortage. Therefore, in order to highlight the strengths of using a multi-attribute approach for planning the PVSP, this paper assumes that at any time, the public health decision-maker’s preferences for uncertain choices involving different levels of any one of the three attributes (impact of a vaccine shortage, coverage levels, or cost) are independent of the values taken by the other two attributes. Therefore, attributes \( Y_1, Y_2, \) and \( Y_3 \) will be considered mutually-utility independent [3, 8, 15] (see the Appendix for a more formal justification), and the proposed form for \( U(Y_1, Y_2, Y_3) \) is given by

\[
1 + KU(Y_1, Y_2, Y_3) = (Kk_1U_1(Y_1) + 1) (Kk_2U_2(Y_2) + 1) (Kk_3U_3(Y_3) + 1),
\]

where \( K \) is the nonzero solution to the equation

\[
1 + K = (1 + Kk_1)(1 + Kk_2)(1 + Kk_3),
\]

\( U_i(Y_i) \) represents the individual utility function of attribute \( i \), and \( k_i \) is the attribute’s scaling constant. By definition, each scaling constant \( k_i \) corresponds to the value of \( U(Y_1, Y_2, Y_3) \) when attribute \( i \) is at its most useful level, and the other two attributes are kept at their least useful levels [15].

3. Decomposition of the utility functions. This section presents mathematical expressions for \( Y_1, Y_2, \) and \( Y_3 \) as well as for their individual utilities. The value of each attribute \( Y_i \) is a function of \( I_j \), the stockpile level of vaccine \( j \in L \) at the beginning of the next fiscal year; hence, \( Y_{ij} \) represents the contribution towards attribute \( Y_i \) of the PVSP provided by the stockpile level of vaccine \( j \). Therefore, \( Y_i = f(Y_{i1}, Y_{i2}, ..., Y_{iL}) \), and hence, its utility, \( U_i(Y_i) \), is itself a multi-attribute utility function.

3.1. Utility of \( Y_1 \) and \( Y_2 \). Without loss of generality, given a PVSP composed of vaccines each offering distinct antigens, a change in the vaccine stockpile contribution to attributes 1 and 2 for any particular vaccine does not affect other vaccine stockpile contributions. Therefore, it can be assumed that the contributions of the stockpile level of vaccine \( j \) towards these attributes are mutually-utility independent of the contributions of the stockpiles of other vaccines. Moreover, due to the distinct offering of antigens of each vaccine in the PVSP, the values of \( Y_{ij} \) are also assumed to be mutually additive independent for all possible attributes. See Appendix for a complete justification.

Keeney and Raiffa [15] propose a multi-attribute utility function form for situations where the attributes are not only mutually-utility independent, but also, additive independent. Therefore, applying Keeney and Raiffa’s expression for the attributes in the vaccine ordering problem leads to

\[
U_i(Y_i) = \sum_{j \in L} \psi_j U_{ij}(Y_{ij}), \quad i = 1, 2,
\]

where \( \sum_{j \in L} \psi_j = 1 \), and \( U_{ij}(Y_{ij}) \) represent the individual utility function of the contribution towards attribute \( i \) provided by the stockpile of vaccine \( j \) at the beginning of the next fiscal year. The scaling constant \( \psi_j \) (0 \( \leq \psi_j \leq 1 \)) is the relative
importance of vaccine based on the morbidity and mortality of the diseases that it prevents. In the following discussion, \( Y_{ij} \) is first defined for \( i = 1, 2 \), and then a definition for \( Y_3 \) is provided.

### 3.1.1. Utility of \( Y_{1j} \)

The impact of a vaccine shortage can be quantified in several different ways; for example, by the total number of children not immunized according to the RCIS, by the corresponding cost of such incomplete immunization, or by the number of children who will be infected by preventable diseases. Without loss of generality, assume that the impact of a supply shortage for vaccine \( j \), \( Y_{1j} \), is a proxy for the dollar value of the maximum backlogged demand occurring during a vaccine shortage, given that the vaccine stockpile level available at the beginning of the shortage is \( I_j \). A large initial vaccine stockpile \( I_j \) can provide vaccine doses during longer vaccine supply interruptions, and hence, its corresponding impact value \( Y_{1j} \) is low. On the other hand, if there is a low initial vaccine stockpile level, then the corresponding impact value of a vaccine shortage will be high. Consequently the maximum size of the backlogged demand, the opportunity cost for each backlogged vaccine dose, and the likelihood of the supply interruption all determine the impact of a supply shortage for a vaccine.

In order to quantify the impact of a vaccine shortage, Jacobson et al. [13, 14] capture a vaccine’s supply and demand characteristics in a stochastic vaccine supply interruption model, which reduces the risk of a shortage for a vaccine when a supply interruption occurs. In their model, Jacobson et al. [13, 14] assume that the length of such a supply interruption, \( T \), is a random variable, and propose an estimator for the minimum vaccine stockpile level during a vaccine shortage. An expanded description of this model is presented in the Appendix.

Given that the number of doses required to provide full immunity is fixed, and the birth rate in the United States changes slowly over time, and hence is fairly constant over any moderate time period, the variability in vaccine demand can be assumed to negligible. Let \( G(I_j, T) \) represent the maximum backlogged demand during a vaccine shortage for an interruption of length \( T \) days, when the initial vaccine stockpile level at the beginning of the supply interruption is \( I_j \), and \( T \) is sufficiently large for a shortage to occur. Therefore, the impact of a potential vaccine shortage is defined by the economic value of the vaccine stockpile level \( G(I_j, T) \). Since the occurrence of a vaccine supply interruption in a given fiscal year is uncertain, then for a given value of \( I_j \), the proposed form for the impact of a potential vaccine shortage results in the random variable

\[
Y_{1j} = |G(I_j, T)|p_j\xi_j,
\]

where \( p_j \) is the purchase price of a dose of vaccine \( j \), and \( \xi_j \) is a Bernoulli random variable with parameter \( \Theta_j \), which corresponds to the probability that a supply interruption occurs for vaccine \( j \) during a given fiscal year. The particular form of \( G(I_j, T) \) is included in the Appendix.

The vaccine stockpile level \( I_j \) at the beginning of the next fiscal year corresponds to \( I_j = I_{oj} + x_j - w_j \), where \( I_{oj} \) is the expected inventory level at the end of the current fiscal year, \( x_j \) is the number of doses of vaccine \( j \) added to the vaccine stockpile at the beginning of the next fiscal year, and \( w_j \) is the number of doses of vaccine \( j \) that the public health decision-maker plans to immediately release from the vaccine stockpile, in order to increase coverage.

The form for \( U_{1j}(Y_{1j}) \) is a consequence of several assumptions. First, at the time of ordering, the decision-maker is more willing to increase the stockpile levels for
those vaccines whose current stockpiles provide lower levels of protection against vaccine shortages, than those whose stockpiles provide higher levels of protection. Second, the marginal utility of increasing vaccine stockpile levels decreases as \( Y_{1j} \) moves closer to zero (i.e., as the impact of the potential vaccine shortage gets closer to zero). These assumptions suggest that \( U_{1j}(Y_{1j}) \) is concave with respect to \( Y_{1j} \), and hence, the decision-maker is risk averse towards reducing the impact of a vaccine shortage [8]. The proposed utility function for \( Y_{1j} \) is provided in the Appendix.

3.1.2. Utility of \( Y_{2j} \). Increasing coverage by releasing vaccines from the stockpiles can improve the vaccination levels against a disease, and hence, it is in the public interest to increase available stockpile levels. At the beginning of each fiscal year, the coverage level that could be acquired by the end of the fiscal year using doses released from the PVSP is defined as the potential coverage level. Therefore, at the beginning of the next fiscal year, the potential coverage level against disease \( j \) is given by the proportion of the population immunized (with a vaccine for \( j \)) until the end of the current fiscal year plus the proportion of the population that could be immunized using doses released from the vaccine stockpiles. Therefore, the potential coverage against disease \( j \) at the beginning of the next fiscal year is given by

\[
Y_{2j} = \frac{v_j P_o + w_j / C_j}{P'}
\]

where \( v_j \) is the expected proportion of the population immunized against disease \( j \) at the end of the current fiscal year, \( P_o \) is the size of the population during the current fiscal year (that could be immunized with doses from the PVSP), \( P' \) is the size of this population in the next fiscal year, \( C_j \) is the number of doses of vaccine \( j \) required to provide full immunization to a child, and \( w_j \) is a decision variable representing the volume of vaccine \( j \) released from the stockpile. In (5), \( v_j P_o / P' \) accounts for changes in population size between the current and next fiscal year. Moreover, the volume of vaccines released from the stockpile cannot exceed the amount of vaccines available at the beginning of the fiscal year, and hence,

\[
w_j \leq I_{oj} + x_j.
\]

Although achieving 100\% coverage level is a desirable public health goal, it is neither practical nor necessary, since the same protective effect can be obtained by immunizing a smaller proportion of the population. In fact, the herd immunity level \([1]\) corresponds to the smallest fraction of a population that must be immunized against a disease such that unvaccinated individuals are protected against the disease. Therefore, it is assumed that public health decision-makers are interested in increasing the coverage level against a pediatric disease, \( Y_{2j} \), up to the herd immunity level \( q_j \). The proposed utility function for \( Y_{2j} \) is provided in the Appendix.

3.2. Utility of \( Y_3 \). For a given purchasing budget, \( \Omega \), the total purchase savings is given by

\[
Y_3 = \Omega - \sum_{j \in L} x_j p_j,
\]

where \( \Omega \geq \sum_{j \in L} x_j p_j \), with \( p_j \) the price per dose of vaccine \( j \). The proposed utility function of \( Y_3 \) is provided in the Appendix.
3.3. **Expected utility.** Given that the occurrence of a vaccine shortage is uncertain, and attribute $Y_1$ is stochastic, the objective of the vaccine ordering problem is to maximize the expected value of $U(Y_1, Y_2, Y_3)$. Considering that the sources of randomness in the vaccine ordering problem are the occurrence and length of the supply interruption ($\xi_j$ and $T$, respectively), and that by definition, $U_2(Y_2)$ and $U_3(Y_3)$ are independent of $\xi_j$ and $T$, then from (1),

$$E[U(Y_1, Y_2, Y_3)] = \frac{(Kk_1 E[U_1(Y_1)] + 1)(Kk_2 U_2(Y_2) + 1)(Kk_3 U_3(Y_3) + 1)}{K} - 1. \quad (8)$$

Moreover, from (3),

$$E[U_1(Y_1)] = \sum_{j \in L} \psi_j E[U_{1j}(Y_{1j})]. \quad (9)$$

For clarity, the actual description of $E[U_{1j}(Y_{1j})]$ is provided in the Appendix.

In the following sections the vaccine ordering problem resulting from using the expressions for $Y_1, Y_2, Y_3$ and their associated utility functions is referred to as the VOP.

4. **Illustrative example.** This section reports computational results for maximizing the expected utility of the VOP for different vaccine supply scenarios, over a range of risk tolerances that resemble risk profiles of potential public health decision-makers. These scenarios describe the conditions under which vaccine order sizes are obtained. Since preferential and risk data about the behavior of decision-makers are hypothetical, the results presented in this section serve to illustrate the type of data required for solving a realistic VOP, and also depicting the type of results that the proposed framework could provide. This discussion begins with a description of the experimental assumptions and the values for the parameters used to solve the VOP.

4.1. **Experimental assumptions and parameters.** The relative importance of a vaccine $j$, $\psi_j$, based on the morbidity and mortality of the diseases prevented by the vaccine is needed to compute $U_1(Y_1)$ and $U_2(Y_2)$, and hence, $E[U(Y_1, Y_2, Y_3)]$. The values for $\psi_j$ are constructed from data presented by Zhou et al. [25], who provide a comprehensive economic evaluation of the importance of seven recommended pediatric vaccines. Zhou et al. [25] use a consistent set of methods and assumptions to make adequate comparisons of the direct and indirect morbidity and mortality costs resulting from not having vaccination programs for seven of the routinely recommended pediatric vaccines during the lifetime of a hypothetical cohort of 3.8 million infants. The value of $\psi_j$ ($0 \leq \psi_j \leq 1$) results from the ratio between the costs induced by not having vaccine $j$ and the costs of having no vaccines in the PVSP. The sixth column of Table 1 provides the values for $\psi_j$ constructed from the results in Zhou et al. [25]. The last column in Table 1 depicts the federally negotiated prices per vaccine dose as of September 2007 [6]. Although there are thirteen vaccines in the PVSP [24], for experimental purposes, this paper assumes that the PVSP consists only of the vaccines displayed in Table 1, for which their relative importance can be established. It is important to remark that Zhou et al.[25] do not rank order vaccines in terms of importance, as their study is not a dynamic transmission model.

Table 2 provides the range of herd immunity levels for the vaccines listed in Table 1, as provided by the Centers for Disease Control and Prevention [7], with the exception of the herd immunity levels for *Haemophilus* influenza type B, hepatitis
Table 1. Pediatric Vaccines

<table>
<thead>
<tr>
<th>Vaccine Reference Number</th>
<th>Vaccine Name</th>
<th>Pediatric Disease(s)</th>
<th>$C_j$ (doses)</th>
<th>$I_{sj}$ (doses)</th>
<th>$\psi_j$</th>
<th>Price per dose (Fed. Negotiated) ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IPV</td>
<td>Polio</td>
<td>4</td>
<td>$8M$</td>
<td>0.105</td>
<td>11.06</td>
</tr>
<tr>
<td>2</td>
<td>MMR</td>
<td>Measles-Mumps-Rubella</td>
<td>2</td>
<td>$4M$</td>
<td>0.169</td>
<td>17.60</td>
</tr>
<tr>
<td>3</td>
<td>HiB</td>
<td>Haemophilus Influenza type B</td>
<td>4</td>
<td>$8M$</td>
<td>0.058</td>
<td>8.12</td>
</tr>
<tr>
<td>4</td>
<td>HBV</td>
<td>Hepatitis B</td>
<td>3</td>
<td>$6M$</td>
<td>0.027</td>
<td>9.10</td>
</tr>
<tr>
<td>5</td>
<td>DTaP</td>
<td>Diphtheria-Tetanus-Pertussis</td>
<td>5</td>
<td>$10M$</td>
<td>0.615</td>
<td>12.65</td>
</tr>
<tr>
<td>6</td>
<td>VAR</td>
<td>Varicella</td>
<td>1</td>
<td>$2M$</td>
<td>0.025</td>
<td>59.15</td>
</tr>
</tbody>
</table>

$C_j$: number of doses in the RCIS, $I_{sj}$: 6-month recommended stockpile level, $\psi_j$: vaccine relative importance

B and varicella, whose values were estimated from Coen et al. [10], Whalley et al. [23], and Anderson and May [1], respectively. The upper bound for the herd immunity values for each pediatric disease was used.

Table 2. Herd Immunity Levels

<table>
<thead>
<tr>
<th>Diseases, $j$</th>
<th>$q_j$ range</th>
<th>Diseases, $j$</th>
<th>$q_j$ range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>0.83-0.86</td>
<td>Pertussis</td>
<td>0.92-0.94</td>
</tr>
<tr>
<td><em>Haemophilus</em> influenza type B</td>
<td>0.04-0.69</td>
<td>Polio</td>
<td>0.80-0.86</td>
</tr>
<tr>
<td>Measles</td>
<td>0.92-0.94</td>
<td>Mumps</td>
<td>0.75-0.86</td>
</tr>
<tr>
<td>Rubella</td>
<td>0.83-0.85</td>
<td>Hepatitis B</td>
<td>0.80-0.86</td>
</tr>
<tr>
<td>Varicella</td>
<td>0.85-0.90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The vaccine manufacturing characteristics introduced in Jacobson et al. [13, 14] to describe the vaccine manufacturer behavior during a supply interruption are assumed to hold, with the associated parameters given in Table 3, as per the definitions in the Appendix. The annual rate of a vaccine supply interruption $\Theta_j$ is estimated to be 0.15 for all vaccines in the PVSP, based on the list of production related vaccine supply interruptions reported by the CDC [5]. Finally, the length of a vaccine supply interruption $T$ is assumed to be exponentially distributed with mean 120 days.

For illustrative purposes, the VOP is solved for risk tolerance values that describe hypothetical decision-makers whose $U_1(Y_1)$, $U_2(Y_2)$, and $U_3(Y_3)$ are concave. The problem instances are solved for an average purchasing budget level $\Omega$, based on historical information available from the Vaccine for Children Program [24].

Equation 1 in Section 2.2 requires scaling coefficients associated with each attribute. Two sets of scaling coefficients $\{k_1, k_2, k_3\}$ can be used to depict the preferential behavior of different public health decision-makers. Each combination of coefficients indicates that the main goal of the PVSP is to minimize the impact of a vaccine shortage. However, one of the combinations intends to capture the preferences of a public health decision-maker who is highly devoted to satisfy the
Table 3. Vaccine Manufacturing Supply Scenario.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>Average US birth rate</td>
<td>11,100 births/day</td>
</tr>
<tr>
<td>( t_M )</td>
<td>Time, after end of interruption, required to achieve maximum production capacity</td>
<td>60 days</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Ratio of the maximum production rate to the effective demand rate</td>
<td>1.1</td>
</tr>
<tr>
<td>( u(t) )</td>
<td>Production ramp-up function</td>
<td>Concave</td>
</tr>
</tbody>
</table>

The main goal of the PVSP (i.e., high concentrated preferences) and gives minimal attention to improving attributes \( Y_2 \) and \( Y_3 \). The second combination of coefficients describes a public health decision-maker that besides focusing on the main goal, is also willing to improve attributes \( Y_2 \) and \( Y_3 \); this decision-maker is said to have mild concentrated preferences. The population considered in this study, \( P_o \), represents the cohort of all children under 5 years of age.

The VOP was solved for different initial conditions of inventory and coverage levels. These initial conditions are presented as factors of the recommended stockpile levels and of the herd immunity, respectively. The expected vaccine stockpile level at the beginning of a given fiscal year corresponds to \( \gamma I_{sj} \), and the initial coverage level of vaccine \( j \) corresponds to \( \zeta q_j \). The values of \( I_{sj} \) and \( q_j \) are given in Tables 1 and 2, respectively. For each combination of \( \gamma \), \( \zeta \), and \( \{k_1, k_2, k_3\} \), the VOP was solved and the following results were recorded: \( E[U(Y_1, Y_2, Y_3)] \), the optimal order sizes of vaccines to include in the vaccine stockpiles, the optimal number of doses to be released from the vaccine stockpile, and the total purchase cost. Table 4 provides experimental values of all the parameters used to analyze the eight potential scenarios resulting from the combinations of \( \{k_1, k_2, k_3\} \), \( \gamma \), and \( \zeta \).

Table 4. Assumptions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Omega )</td>
<td>$140M</td>
</tr>
</tbody>
</table>
| \( \{k_1, k_2, k_3\} \) | High preference: \{0.900, 0.075, 0.010\}  
                      Mild preference: \{0.500, 0.350, 0.100\} |
| \( \gamma \) | \{0.20, 1.00\} |
| \( \zeta \) | \{0.40, 0.95\} |
| \( P_o \) | 20M children |
| \( P' \) | \((1.0 + 0.009/5) \times P_o\) children |

Cohort growth, \( P' \), is based on US pop. growth, CIA World Factbook

For each of the resulting experimental scenarios, the VOP was solved using the Differential Evolution algorithm [20] implemented in Mathematica 5.2, with a working precision of eight significant figures, and a maximum number of 10,000 iterations executed per problem. To avoid getting trapped at a local optimum, each instance of the utility maximization problem was solved for several different randomly generated initial solutions.
4.2. Results. For each experimental scenario resulting from the combinations of \{k_1, k_2, k_3\}, \gamma, and \zeta, Table 5 reports the values for the best VOP solutions. As a benchmark, the fourth column of Table 5 also depicts the utility value for a baseline strategy applied to each of the experimental scenarios. This baseline strategy occurs when public health decision-makers choose to divide the entire available budget among the different vaccines in the PVSP based on the cost of increasing their coverage level by 1%. Moreover, for the baseline strategy, the public health decision-maker does not release vaccines for improving coverage. Figures 1 to 4 graphically depict data from Table 5.

Figure 1 shows that unless the initial conditions for the vaccine stockpile inventory and immunity levels are excellent (i.e., \gamma = 1.0, \zeta = 0.95), in all other scenarios, ordering additional vaccine doses is required primarily for vaccines that have greater relative importance among those included in the PVSP, as indicated by \psi_j (i.e., vaccines: 5=DTaP, 2=MMR, 1=IPV). Moreover, the larger the number of doses ordered for these vaccines, the larger the number of doses released to increase coverage levels. Figure 2 also shows that, in general, more vaccines doses should be released and used to increase coverage if the initial available inventory is high. In the case of having excellent initial inventory and coverage conditions (i.e., \gamma = 1.0, \zeta = 0.95), the decision-maker should not only release vaccines from the stockpiles but must avoid ordering additional vaccines.

Figure 3 shows that the VOP solutions provide higher expected utility values than those obtained by using the baseline solutions. On average, when the initial inventory levels are low (i.e., \gamma = 0.2), the expected utility of the VOP solutions
### Table 5. VOP Solutions.

| $\gamma$ | $\zeta$ | Preference | $U(Y_1, Y_2, Y_3)$ | Cost ($\text{M}$$)$ | $w_1$ | $w_2$ | $w_3$ | $w_4$ | $w_5$ | $w_6$ | $x_1$ | $x_2$ | $x_3$ | $x_4$ | $x_5$ | $x_6$ |
|----------|--------|------------|---------------------|---------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|
|          |        | baseline   | $E[U(Y_1, Y_2, Y_3)]$ | optimal             |      |      |      |      |      |      |      |      |      |      |      |      |      |
| 0.4      | mild   | 0.618      | 0.922               | 51.72               | 0.03 | 0.02 | 0.03 | 0.03 | 4.11  | 0.00 | 0.00 | 0.00 | 0.00 | 4.07 | 0.00 |
|          | high   | 0.651      | 0.983               | 70.14               | 0.09 | 0.05 | 0.14 | 0.06 | 5.38  | 0.01 | 0.06 | 0.04 | 0.11 | 0.04 | 5.34 | 0.00 |
| 0.2      | mild   | 0.695      | 0.997               | 9.11                | 0.03 | 0.02 | 0.03 | 0.02 | 0.76  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.72 | 0.00 |
|          | high   | 0.669      | 0.999               | 11.31               | 0.20 | 0.02 | 0.03 | 0.50 | 0.44  | 0.01 | 0.17 | 0.00 | 0.47 | 0.40 | 0.00 |
| 0.95     | mild   | 0.372      | 0.945               | 40.48               | 6.43 | 3.23 | 6.43 | 4.82 | 11.22 | 1.61 | 0.00 | 0.01 | 0.00 | 0.00 | 3.18 | 0.00 |
|          | high   | 0.226      | 0.988               | 43.98               | 6.47 | 3.30 | 6.43 | 4.94 | 11.26 | 1.61 | 0.04 | 0.00 | 0.11 | 3.22 | 0.01 |
| 1.0      | mild   | 0.446      | 0.645               | 0.0                 | 0.89 | 0.97 | 0.72 | 0.89 | 0.97  | 0.93 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
|          | high   | 0.242      | 0.405               | 0.0                 | 0.89 | 0.97 | 0.72 | 0.89 | 0.97  | 0.93 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

$w_i$ and $x_i$ for $i = \{1: \text{IPV}, 2: \text{MMR}, 3: \text{Hib}, 4: \text{HBV}, 5: \text{DTaP}, 6: \text{VAR}\}$
Figure 2. Number of doses released for the best VOP solutions, \(w_i\) with \(i = \{1 : \text{IPV}, 2 : \text{MMR}, 3 : \text{HPV}, 4 : \text{HBV}, 5 : \text{DTaP}, 6 : \text{VAR}\}\)

is 31% higher than the corresponding solution provided by the baseline strategy. When the initial inventory levels are high and initial coverage levels are low (i.e., \(\gamma = 1.0, \zeta = 0.4\)), the expected utility of the VOP solutions is on average 66% higher. Interestingly, when the initial conditions for the inventory and immunity levels are excellent (i.e., \(\gamma = 1.0, \zeta = 0.95\)), the expected utility of the VOP solutions is lower than the values obtained for any other experimental scenario. This seemingly contradictory result is due to the fact that under this initial condition, no orders are incorporated into the vaccine stockpile, while doses are released for all vaccines. Therefore, the resulting expected utility is bounded only by the utility gains from improving the incremental coverage level \(Y_2\).

The choice of decision-maker affects the expected utility values of the solutions of the VOP. In fact, when the experimental scenarios have high coverage levels, a decision-maker with mild concentrated preferences (i.e., \(\{k_1, k_2, k_3\} = \{0.50, 0.35, 0.10\}\)) is easier to satisfy than a public health decision-maker with high concentrated preferences (i.e., \(\{k_1, k_2, k_3\} = \{0.90, 0.075, 0.01\}\)). There is no observable difference in behavior for scenarios with low coverage levels.

In terms of purchasing costs, Figure 4 shows that even under lower levels of financial concern (i.e., the relative importance of \(Y_3\) given by \(k_3 = 0.01\) and \(k_3 = 0.10\) for the high and mild preferences, respectively), there was no experimental scenario in which the VOP solution required spending the entire allocated budget of $140M. Moreover, the VOP solutions for scenarios under the best initial conditions required that no budget be spent for purchasing vaccines.

5. **Conclusions.** This paper introduces a flexible framework for integrating the conflicting objectives of health care decision-makers into building pediatric vaccine
Figure 3. Expected utility for the best VOP solutions

Figure 4. Purchasing costs for the best VOP solutions

stockpiles that are more cost-effective and robust towards risk. A set of important
attributes that must be considered when deciding the number of doses for replenishing the pediatric vaccine stockpiles is identified. A set of utility functions is also proposed, based on the knowledge of the vaccine supply chain.

A set of eight experimental scenarios was used to illustrate the type of results and data that can be obtained from the proposed framework. Note that the reported results cannot be considered conclusive. However, the study’s illustrative example demonstrates practical benefits of vaccine stockpile policies that result from a strong collaboration between vaccine manufacturers and public health decision-makers. Actual results will vary depending on the actual risk tolerance of the public health decision-maker and on the attributes that are currently of interest.

Experimental results suggest that despite having a clear preference for minimizing the impact of a vaccine shortage, managing pediatric vaccines stockpiles should not be limited to increasing stockpile levels, but rather, to actively using vaccine doses to increase coverage. The illustrative example indicates that a vaccine stockpile should not be seen as a repository of vaccines, but rather, as a repository of opportunities for gaining coverage that could effectively protect society. Clearly, having a larger stockpile of pediatric vaccines does not necessarily increase coverage but rather the potential to increase it. Since vaccine shortages are infrequent events, the experimental model suggests using the stockpile to more quickly achieve desired herd immunity levels. More importantly, small financial considerations by public health decision-makers can have a major impact on vaccine stockpile policy. For the (assumed) small relative importance of purchase savings, \( Y_3 \), as given by the values for \( k_3 \), the highest expected utility values never required spending the entire available budget.

Several elements of pediatric vaccination can enhance the VOP outlined in this paper. For instance, as noted by an anonymous reviewer, most pediatric vaccinations (unlike influenza) are not annual and therefore risks and benefits accrue over many years; a vaccine shortage in one year does not mean that a given patient is never vaccinated. Therefore, the patient may experience a delay of one or several years in receiving the vaccine. Using multi-period utility functions with the VOP may quantify the cost of such a delay.

An interesting variation in modeling the VOP is to measure the impact of a potential vaccine shortage in terms of the number of fatalities, or in terms of QALY's (i.e., quality-adjusted life-years) and then consider potential immunity as the result of long term vaccination. Since the effect of vaccination is long lasting, the VOP could be seen as a multi-period and multi-attribute problem.

This study serves as an invitation to public health decision-makers and vaccine manufacturers to re-engineer the objectives of having pediatric vaccine stockpiles and establish flexible policies for maximizing the expected utility of such public health assets.

Appendix.

Description of the vaccine supply interruption model. Jacobson et al. [13, 14] translate the vaccine’s supply and demand characteristics into a vaccine supply interruption model that combines the knowledge of the manufacturers’ production rate and the vaccine demand to define the risk of a shortage of a vaccine \( j \) that requires \( C_j \) doses to provide full immunization, with all these antigens sharing the same immunization schedule. When a vaccine \( j \) suffers a supply interruption, the initial vaccine stockpile level, \( I_j \), becomes depleted at rate \( C_j \alpha \lambda \) doses per day. The
length of such a supply interruption is a random variable $T$ with pdf $f(T)$, $\alpha$ is the desired vaccination coverage rate, and $\lambda$ is the population birth rate per day. At time $t = T$, the vaccine production operation is restored at a rate $u(t)$ increasing from zero to a maximum production capacity rate $\beta C_j \alpha \lambda$, which is maintained until the vaccine stockpile is replenished to $I_j$ doses; the value of $\beta$ corresponds to the ratio between the maximum supply rate and the demand rate. The maximum supply rate is achieved in $t_M$ days after production is restored (i.e., $u(T + t_M) = \beta C_j \alpha \lambda$). Jacobson et al. [13, 14] consider that production interruptions for the same vaccine are assumed to occur sufficiently far apart (i.e., several years) such that the replenishment process can occur.

Expression for $G(I_j, T)$. The expression for $G(I_j, T)$ is based on the Vaccine Supply Interruption Model described in the first part of this Appendix. It is important to remark that for the current study, it is assumed that the demand variability is negligible, demand occurs at any point in time, and that the time reference starts with zero when a supply interruption period begins.

The function $S(t|T)$ represents the vaccine supply function at time $t$, given that the interruption period lasts $T$ days. Based on the form of $u(t)$, the function $S(t|T)$ is defined by

$$S(t|T) = \begin{cases} I - C\alpha \lambda t & 0 \leq t \leq T, \\ I - C\alpha \lambda t + \int_0^t u(\tau) d\tau & T < t \leq T + t_M, \\ I - C\alpha \lambda t + \int_T^{T+t_M} u(\tau) d\tau + \beta C\lambda (t - t_M) & T + t_M \leq t. \end{cases}$$

(10)

Let $G(I_j, T)$ be the lowest stockpile level during a vaccine shortage, given that the initial stockpile level is $I_j$, and that the length of the supply interruption is large enough for a shortage to occur. The value of $t_m$ corresponds to the value of $t$, after production is restored, such that $dS(t|T)/dt = 0$. Therefore,

$$t_m = \left( \frac{\alpha}{\beta} \right)^{\frac{1}{2}} t_M + T,$$

and $G(I_j, T)$ is equal to the value of $S(t_m|T)$ when $I = I_j$.

Jacobson et al. [13, 14] show that for the supply interruption model described above, once production is restored, the expected vaccine stockpile level further decreases by $\delta(t_m)$ until the expected vaccine stockpile level starts increasing, where $\delta(t_m)$ corresponds to the net cumulative vaccine supply and demand between the end of the interruption period (i.e., $t = T$), and the time when the vaccine stockpile level is at its minimum (i.e., $t_m$). Moreover, $\delta(t_m)$ can be shown to be negative, and independent of $T$ and $I_j$ [13].

Mutually-utility independence of $Y_1$, $Y_2$, $Y_3$. Following the procedure presented by Beroggi [3], let $V = \{y_1, y_2, y_3\}$ be a set of attribute values provided by the stockpile levels of a vaccine package, such that $Y_1 = y_1, Y_2 = y_2, Y_3 = y_3$, and $V_j$ is a decomposition of $V$ such that $V_j \subset V$ and $V_j \neq \emptyset$. Independent of the number of attributes in the decomposition of $V_j$, when the attributes containing $V_j$ take on fixed values, then the complement can be referred to as $\overline{V_j}_\delta$, where $\delta$ is the label for the assumed attribute values (e.g., if $\overline{V_1} = \{y_2 = 0.7, y_3 = $120M$\}$, then $\delta = \{y_1, 0.7, $120M$\}$ for any $y_1$).
Under the two assumptions provided in Section 2.2, it can be assumed that the decision-maker’s preference relation between lotteries for any decomposition \( V_j \) is expressed as
\[
[(V_j, V_{j\delta}), p, (V_k, V_{k\delta})] \succeq [(V_r, V_{r\delta}), p, (V_s, V_{s\delta})]
\]
\[\iff [(V_j, V_{j\tau}), p, (V_k, V_{k\tau})] \succeq [(V_r, V_{r\tau}), p, (V_s, V_{s\tau})]
\]
where \( V_j \neq V_k \neq V_r \neq V_s \), \( \delta \neq \tau \) and the notation \( [A, p, B] \) represents a binary lottery with \( A \) occurring with probability \( p \), and \( B \) with probability \( 1 - p \) [3]. Therefore, attributes \( Y_1, Y_2 \), and \( Y_3 \) are mutually-utility independent [3, 8, 15].

Additive independence of \( Y_{ij} \). Given that \( Y_{ij} \) is mutually-utility independent of any other \( Y_{ip} \), for all vaccines \( j, p \in L \), let \( Z = \{Y_{i1},...,Y_{ij},...,Y_{iL}\} \) be the set of contributions towards attribute \( i \) for all vaccines in the PVSP, where \( Z_k \) is a decomposition of \( Z \) such that \( Z_k \subset Z \), \( Z_k \neq \emptyset \), with \( Z_k \neq Z \) and \( \overline{Z_k} = Z \setminus Z_k \). Then, assume that for any decomposition \( k \), the decision-maker shows indifference \( (\sim) \) between the lotteries
\[
[(Z_k^+, \overline{Z_k^+}), 0.5, (Z_k^-, \overline{Z_k^-})] \text{ and } [(Z_k^+, \overline{Z_k^-}), 0.5, (Z_k^-, \overline{Z_k^+})],
\]
where \( Z_k^+ \) means the highest contribution of the decomposition towards attribute \( i \), while \( Z_k^- \) means the lowest contribution. Therefore, the values of \( Y_{ij} \) can be assumed to be additive independent of each other [15, 11].

Utility function for \( Y_{1j} \). The proposed utility function is given by
\[
U_{1j}(Y_{1j}) = \begin{cases} 
1 - \exp \left( -\frac{Y_{1j} - Y_{1j}^*}{R_1} \right) & \text{ if } Y_{1j} < Y_{1j}^* \\
1 - \exp \left( -\frac{Y_{1j}^*}{R_1} \right) & \text{ if } Y_{1j} \geq Y_{1j}^*, \end{cases} \tag{12}
\]
where \( R_1 \) represents the risk tolerance to \( Y_1 \), and \( Y_{1j}^* \) is the impact value after which \( U_{1j}(Y_{1j}) = 0 \). For example, \( Y_{1j}^* \) could be defined as the impact of a potential vaccine shortage caused by a two-year supply interruption when the initial stockpile level was zero, with any impact \( Y_{1j} \) larger than \( Y_{1j}^* \) having an associated utility of zero. Note the value of \( U_{1j} \) is bounded between 0 and 1, with \( U(Y_{1j}^*) = 0 \) and \( U_{1j}(0) = 1 \).

Utility function of \( Y_{2j} \). Assuming that the decision-maker is risk averse towards \( Y_{2j} \), and has a constant risk aversion, then the proposed form for the utility of the coverage level of vaccine \( j \) is given by
\[
U_{2j}(Y_{2j}) = \frac{1 - \exp \left( -\frac{Y_{2j}}{R_2} \right)}{1 - \exp \left( -\frac{q_j}{R_2} \right)}, \quad \text{and } Y_{2j} \leq q_j, \tag{13}
\]
where \( R_2 \) is the risk tolerance for the attribute \( Y_2 \), which is bounded above by \( q_j \). Note that by definition, \( U_{2j}(Y_{2j}) \) is bounded between 0 and 1, with \( U_{2j}(0) = 0 \) and \( U_{2j}(q_j) = 1 \).
Utility function for $Y_3$. Let the utility of the cost savings $Y_3$ be denoted by the function $U_3(Y_3)$, such that when the entire budget is consumed and there are no cost savings (i.e., $Y_3 = 0$), then $U_3(0) = 0$; while in the ideal case when the entire budget is saved (i.e., $Y_3 = \Omega$), then $U_3(\Omega) = 1$. Moreover, assume that the decision-maker shows a constant risk aversion towards cost savings. Therefore, based on the previous assumptions, the utility of $Y_3$ is

$$U_3(Y_3) = \frac{1 - \exp \left(-\frac{Y_3}{R_3}\right)}{1 - \exp \left(-\frac{\Omega}{R_3}\right)},$$

(14)

where $R_3$ is the risk tolerance towards cost savings. Note that the lower the risk tolerance towards cost savings, the more willing the decision-maker is to spend funds purchasing vaccines.

**Expression for $E[U_{1j}(Y_{1j})]$.** Since $\xi_j \sim \text{Bernoulli}(\Theta_j)$, and using the definition of $Y_{1j}$ in (4), then

$$E[U_{1j}(Y_{1j})] = \int_{T_{\text{critical}}}^{\infty} \left( \sum_{r=0}^{1} U_{1j} \left( G(I_j, T)p_j \xi_j \right) P(\xi_j = r) \right) f(T) dT$$

(15)

$$= \int_{T_{\text{critical}}}^{\infty} \left( \Theta_j U_{1j} \left( G(I_j, T)p_j \right) + (1 - \Theta_j) \right) f(T) dT,$$

(16)

where $T_{\text{critical}}$ is defined as the minimum length of a supply interruption that triggers the occurrence of a vaccine shortage. Consequently, $T_{\text{critical}}$ is the length of the vaccine supply interruption for which the initial vaccine stockpile level exactly satisfies the demand during such a supply interruption, and also the additional demand $\delta(t_m)$. Therefore,

$$T_{\text{critical}} \equiv I_j + \frac{\delta(t_m)}{C\alpha \lambda},$$

(17)

where $\delta(t_m)$ is the net change in stockpile level between the time when the production is restored and when the stockpile level begins to increase (i.e., $\delta(t_m) = \int_{T}^{t_m} u(t) - C\alpha \lambda dt$).

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