

USING MONTE CARLO SIMULATION TO ASSESS THE VALUE OF COMBINATION VACCINES FOR PEDIATRIC IMMUNIZATION

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ABSTRACT

Research by vaccine manufacturers has resulted in the development of new vaccines that protect against a number of diseases. This has created a dilemma for how to introduce such new vaccines into an already crowded Recommended Childhood Immunization Schedule and prompted the development of vaccine products that combine several individual vaccines into a single injection. Such combination vaccines permit new vaccines to be inserted into the immunization schedule without exposing children to an unacceptable number of injections during a single clinic visit. This paper describes a Monte Carlo simulation with an integer programming model to assess and quantify the distributions around inclusion prices which reflect the economic premium of these new combinations. Each new vaccine competed against existing vaccines for six childhood diseases (hepatitis B, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, and polio) at their March 2000 Federal contract discount prices.

1 INTRODUCTION

The United States Recommended Childhood Immunization Schedule (CDC 2001) has become increasingly crowded, requiring children to endure a large number of vaccine injections over several years (Weniger et al. 1998). Moreover, vaccine manufacturers have developed and are launching new vaccines for diseases not currently part of the schedule. Such new products will exacerbate this crowding dilemma. Children and parents have limited tolerance for multiple injections during a single clinic visit (Parkman 1995). Parents/guardians may not take the time (and bear the cost) to

make additional visits for deferred vaccinations (Dietz et al. 1994, Lieu et al. 2001). Such noncompliance with recommended vaccine scheduling puts children at increased risk to contract diseases that the vaccines are designed to prevent. This may result in a significant burden and cost to both the family unit and the nation's health-care system.

Several solutions have been proposed to overcome these complications. The ideal would be a single dose oral vaccine that immunizes children at birth for all childhood diseases (Mitchell et al. 1993). A more realistic solution is to develop combination vaccines (Parkman 1995) that combine several individual vaccines into a single injection (CDC 1999), reducing the number of injections and clinic visits needed to comply with the immunization schedule. In addition to reducing the number of injections during any single clinic visit, combination vaccines help make room in the schedule to protect against newly vaccine-preventable diseases by the immunization program. For example, the United States Food and Drug Administration (FDA) approved in 2000 the first pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in infants (CDC 2000, The Medical Letter 2000). Its inclusion in the schedule by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) adds four injections during the first two years of life for the typical child.

Vaccine manufacturers have responded by developing several new combination vaccines. For example, Aventis Pasteur, North American Vaccine (now Baxter), GlaxoSmithKline, and Wyeth-Lederle have worked to develop various pentavalent and hexavalent combination vaccines that immunizes against five or even all six of the diseases diphtheria, tetanus, pertussis, *Haemophilus influenzae* type

b, hepatitis B, and polio. Given the increasing number of combination vaccines that may become available over the next decade, it may be difficult for health care providers and immunization programs to assess the relative value and choose among various existing and new monovalent and combination products to stock in their vaccine inventories. The question is, are the savings in direct medical (clinical) costs and indirect societal (consumers) costs due to reduced numbers of injection resulting from the use of new combinations sufficient to outweigh their potential higher purchase price? New combinations will result in a variety of vaccine formularies of different sizes, with attendant differences in handling and stocking costs, even if they each might satisfy the recommended schedule. Moreover, one can argue that since combination vaccines help make room for preventing new diseases by making room in the schedule, should they be credited with some portion of the savings that result from lower disease incidence? All these questions are difficult to address.

This paper applies Monte Carlo simulation to explore the distribution of economic values determined by an integer programming model for vaccine selection (Jacobson et al. 1999, Weniger et al. 1998). Sewell et al. (2001) introduce an integer programming model incorporating four combination vaccines that may become available in the United States (**DTP_a-HIB-HBV**, **DTP_a-HIB-IPV**, **DTP_a-HBV-IPV**, and **DTP_a-HIB-HBV-IPV**). The model determined the inclusion price at which each of the vaccines would win a place in a lowest-cost formulary that would satisfy the immunization schedule.

The cost of each injection, thus the worth of a combination vaccine that reduces their number, varies based on the circumstances/perspective of health-care providers and parents/guardians. For a given assumed injection cost, there is a maximal inclusion price at which a combination vaccine provides a good economic value (i.e., the highest price at which the combination vaccine earns a place in the lowest-cost vaccine formulary). Monte Carlo simulation of the distributions around these critical injection cost estimates provide a sensitivity analysis for the resulting point estimates of the inclusion prices (Sewell et al. 2001) of the pentavalent and hexavalent vaccines studied, thus providing a more refined estimate of their economic value.

2 MODEL ASSUMPTIONS

The integer programming model developed for this analysis captures the first five years of the Recommended Childhood Immunization Schedule (CDC 2001) for immunization against six childhood diseases: diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, hepatitis B, and polio. The economic impact of four different new vaccine combinations were considered:

- diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, and hepatitis B (**DTP_a-HIB-HBV**),

- diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, and polio (**DTP_a-HIB-IPV**),
- diphtheria, tetanus, pertussis, hepatitis B, and polio (**DTP_a-HBV-IPV**),
- diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, hepatitis B, and polio (**DTP_a-HIB-HBV-IPV**).

These combination vaccines were analyzed by adding them, one at a time, to the list of all twelve vaccine products for the diseases under study which were licensed and under contract for distribution by the Centers for Disease Control and Prevention (CDC) as of March 31, 2000. These vaccines were manufactured by five companies: Aventis Pasteur, Merck, North American Vaccine (now Baxter), GlaxoSmithKline, and Wyeth-Lederle.

The four hypothetical combination vaccines were analyzed in those formulations from various manufacturers reported to have studied them or marketed them already in other countries (Jacobson and Sewell 2002). Since **DTP_a** manufacturer brand matching is required (Jacobson and Sewell 2002), then a total of six different cases for the four combination vaccines had to be studied. For **DTP_a-HIB-HBV** and **DTP_a-HBV-IPV**, there is just one case (GlaxoSmithKline). **DTP_a-HIB-IPV** is linked to four manufacturers. However, since the March 2000 U.S. Federal purchase prices and packaging for existing **DTP_a** were the same across all the manufacturers, the results for any one manufacturer will be the same for any of the other manufacturers in regard to **DTP_a** manufacturer brand matching (see Jacobson and Sewell 2002). The only exception to this is for Aventis Pasteur, which markets a **DTP_a-HIB** combination vaccine. Therefore, the analysis was done separately for matching a new pentavalent or hexavalent vaccine for this manufacturer to its existing **DTP_a**-containing products. Jacobson and Sewell (2002) refer to these two additional cases as the AVP cases.

To provide boundaries for the scope of the results presented, certain assumptions were needed. Wherever possible, the assumptions used in the companion study (Sewell et al. 2001, Jacobson and Sewell 2002) were also used here. The cost (objective) function components that were used to determine the inclusion prices for the four combination vaccines, as well determine the overall cost of the resulting vaccine formularies, included

- the purchase price of all licensed vaccines,
- the cost of each clinic visit,
- the cost of vaccine preparation by medical staff,
- the cost of administering each injection.

There are several other factors that impact the cost of immunization (Weniger et al. 1998). These include cold chain costs (i.e., the cost of providing and maintaining the

cold chain for vaccines that require such storage, as well as the costs associated with cold chain failure), product shelf life and vaccine expiration costs (i.e., the cost of vaccine wastage due to inadequate or poor inventory management), adverse reaction costs (i.e., the cost of treating undesirable side effects associated with vaccination), and the costs associated with vaccine-preventable disease incidence (i.e., the cost of treating the diseases that were not prevented by the vaccines being administered). Unfortunately, reliable data is difficult to secure to support these costs, hence they are not included in the cost function for the integer programming model developed here.

The cost of a clinic visit was set at \$40. This value was used in a previous pilot demonstration of the algorithm (Weniger et al. 1998) to represent fixed per-visit direct and indirect costs associated with an immunization visit to a clinic. The separate cost of vaccine preparation by the medical staff was classified into three categories (with associated preparation times):

- liquid vaccine packaged in pre-filled *syringe* (0.5 minutes)(s),
- liquid vaccine packaged in pre-filled *vial* (1.5 minutes) (v),
- *powdered* (lyophilized) vaccine requiring a reconstitution step (3.0 minutes) (p).

The times for these three categories, labeled (s) for pre-filled syringe, (v) for pre-filled vial, and (p) for powder, were distributed around a reported mean time of 1.6 minutes to administer an injection [10, 18bis]. A medical staff compensation (labor) rate of \$0.50/minute was used before (Weniger et al. 1998), and repeated here. Sewell et al. (2001) provides a list of preparation costs and the Federal discount prices for the twelve existing vaccine products licensed and under contract with the CDC. Note that three of the vaccine products, **HBV** manufactured by GlaxoSmithKline and by Merck, and **IPV** manufactured by Aventis Pasteur, are available in both pre-filled syringes and liquid vial formulations. Though their purchase prices are the same, the pre-filled syringes requires one fewer minute of preparation time, hence from an economic standpoint, would always be chosen over the pre-filled vials. Therefore, for these three vaccine products, only the pre-filled syringes are considered in the analysis.

The cost associated with administering an injection can be broken down into several telescoping components (Weniger et al. 1998). The first component is the actual direct cost of administering the vaccine, which was estimated to be \$5.00 for each injection (Lieu et al. 2000). The second component is the direct cost for repeat clinic visits if injections are refused by the parent/guardian (e.g., when four or more injections are required at a particular clinic visit). This cost is estimated to be \$3.00 for each injection. The third component is the indirect cost of paren-

tal/guardian lost time from work for repeat clinic visits if injections are refused by the parent/guardian. This cost is estimated to be \$12.00 for each injection. The fourth component is the indirect cost of “pain and emotional distress to the child” (hence indirectly to the parent/guardian) associated with each injection, as measured by a parent’s/guardian’s “willingness-to-pay” to avoid such pain. This cost has been estimated as a low of \$10.00 median for reducing injections from 2 to 1 or 0 (Meyerhoff et al. 2001), and a median of \$25.00 each for reductions from a greater number of injections (Meyerhoff et al. 2001, Lieu et al. 2000, Kupermann et al. 2000).

It is difficult to assess a single value/cost associated with administering an injection, since each parent/guardian and health care provider may place widely disparate values on each of the four components described above. Therefore, for a given population of parents/guardians and/or health care providers, one can assign a mean value for the cost associated with administering an injection. The following three perspectives are used to set this mean cost of an injection:

Perspective i) \$5.00 = the marginal direct medical costs. Note that this cost reflects the perspective of the payer (e.g., an HMO or health insurer), but not the parent/guardian and society,

Perspective ii) \$20.00 = cost from Perspective i), plus the direct medical costs associated with repeat clinic visits for deferred injections, plus the indirect cost of parental/guardian lost time from work for repeat clinic visits if injections are refused by the parent/guardian. Note that this cost captures the perspective of both the payer and society as a whole, since it includes the indirect costs of lost work time by parents/guardians,

Perspective iii) \$45.00 = cost from Perspective ii) plus the indirect cost of \$25.00 per injection for “pain and emotional distress.”

The following assumptions are used in this analysis: The Recommended Childhood Immunization Schedule (CDC 2001) was followed for immunization against the six diseases of interest. Injections can be administered in months 0-1 (within one month of birth), 2, 4, 6, 12-18, and 60, providing six opportunities (months/periods) to administer vaccines; only one clinic visit can occur in each of these months/periods; and all injections in a given month/period are administered in a single clinic visit; only the twelve vaccines under Federal CDC contract as of March 2000 are included in the model (plus one of the four combination vaccines under study); **HIB** vaccines can only be administered in month 2 or later; the first **HBV** injection is administered in an outpatient visit in month 0-1; if **HIB** vaccine products by Merck are administered in both months 2 and 4, then no **HIB** vaccine is required in month 6; same-manufacturer brand matching for sequential doses is required for **DTP_a** vaccines, but not for **HIB**, **HBV**, and **IPV** vaccines; extravaccination is permitted for **HBV**,

HIB, and **IPV** vaccines, but not for **DTP_a** vaccines; the **DTP_a-HIB** vaccine by Aventis-Pasteur can only be administered in the 12-18 or 60 month periods; the vaccine prices are the Federally-negotiated discount prices effective March 2000 (use of higher private-sector vaccine prices would produce correspondingly higher inclusion prices).

Note that these assumptions are based on the guidelines as set forth in the Recommended Childhood Immunization Schedule (CDC 2001). Individual situations that deviate from this schedule are not considered, and are beyond the scope of this study.

3 MODEL DESCRIPTION

An integer programming model was developed to determine the inclusion prices for the four different combination vaccines (Sewell et al. 2001). Monte Carlo simulation was then applied in conjunction with this model to estimate the distribution for these inclusion prices for a given population of parents/guardians (as defined by different injection cost distributions).

The decision variables for the integer programming model are all either non-negative integers or binary (0-1). A set of binary decision variables is defined for each month in which a particular vaccine (by manufacturer) can be administered (months 0-1, 2, 4, 6, 12-18, and 60), where a value of one (zero) indicates that the vaccine combination should (not) be administered in that month. The decision variables are also indexed by the particular manufacturer of each vaccine. The resulting integer programming model contains 96 integer variables, of which 90 are binary variables, and 51 constraints. The integer programming model was created using AMPL Plus 1.6 and solved using the CPLEX 6.5 LP and MIP Solver on a Pentium 550Mhz IBM-compatible personal computer. For complete details on the integer programming model, see Jacobson and Sewell (2002).

The Monte Carlo simulation sampled possible injection costs from various distributions, where each distribution corresponded to the potential values that various populations of health-care providers and parents/guardians might place on avoiding an injection. Three different probability distributions for the injection cost were considered, each with three different mean injection costs corresponding to the three perspectives (\$5, \$20, \$45) described in Section 2. To provide a breadth of probability distribution classes, a uniform distribution, a normal distribution, and an exponential distribution for the cost of administering an injection were used. For the uniform distribution case, the distributions used were $U[0, \$10]$, $U[0, \$40]$, and $U[0, \$90]$. For the normal distribution, the distributions used were $N(\mu = \$5, \sigma = \$1)$, $N(\mu = \$20, \sigma = \$4)$, and $N(\mu = \$45, \sigma = \$9)$. For the exponential distribution, the distributions used were exponential with means \$5, \$20, and \$45. It would be very difficult to determine the exact distribution for a population of health-care providers and parents/guardians for the cost of administering

an injection. Therefore, the three distributions were chosen to provide different levels for the coefficients of variation (σ/μ). In particular, the uniform distributions all have coefficients of variation $2/(12)^{1/2} \approx 0.577$ (which is moderate), the normal distributions all have coefficients of variation 0.2 (which is small), and the exponential distributions all have coefficients of variation 1.0 (which is large). Therefore a total of nine Monte Carlo simulation experiments were run for each of the four combination vaccines.

For a given combination vaccine, each Monte Carlo simulation experiment generated a total of 500 vaccine injection costs, where each such cost was used as an input to the integer programming model. The resulting integer programming model was then solved to determine the inclusion price for the combination vaccine such that the resulting vaccine formulary contained this combination vaccine for one, two, or three doses in the schedule. Note that when the two-dose vaccine formulary is not reported, this means that the inclusion price at which the combination vaccine enters the resulting vaccine formulary for two doses and for three doses are the same. Each set of Monte Carlo experiments for each of the combination vaccines took approximately five hours to execute.

The resulting set of inclusion prices for each new combination vaccine was used to create (estimate) the distribution of inclusion prices for the combination vaccines. This distribution can be used, for example, to determine the probability that the population of parents/guardians will choose the combination vaccine (over existing vaccines) at a given inclusion price. Therefore, the inclusion price distribution provides valuable information for vaccine manufacturers, since it provides a tool for estimating the market share that can be secured from a particular population (based on the injection cost distribution). By using different injection cost distributions, the sensitivity of the form of this distribution on the inclusion price distribution can be assessed.

4 METHODOLOGY AND RESULTS

The results of the Monte Carlo simulation experiments for the six different cases described above (Jacobson and Sewell 2002) provide the inclusion price distributions for nine different distributions of injection costs, representing an anticipated range of economic perspectives of health care providers/parents/guardians. This information allows vaccine purchasers such as public health officials and health care providers to compare the offered price of a new vaccine against the inclusion prices calculated at varying percentiles as an indication of the frequency with which it represents a "good buy".

For each of the six combination vaccine cases, and for each of the nine Monte Carlo simulation experiments, the integer programming model was used to solve for 500 inclusion prices for the one dose vaccine formulary and 500 inclusion prices for the two or three dose optimal formulary.

Each of the 500 inclusion prices obtained from the Monte Carlo simulation experiments required the integer programming model to be solved several times. This was done using a bisection search algorithm (Burden and Faires 1997), where an upper and lower bound for the inclusion price of the combination vaccine was set, and based on whether the upper or lower bound resulted in the vaccine entering the optimal formulary, the middle point between the upper and lower bound replaced either the upper or the lower bound.

Each set of 500 inclusion prices was used to compute a mean (X) and a standard deviation (s) for these prices, as well as the 20th percentile inclusion price, the 50th (median) percentile inclusion price, and the 80th percentile inclusion price. At the 20th percentile inclusion price, 20 percent of a population of “rational vaccine purchasers” would still not purchase a new vaccine offered at that price because it does not provide good economic value because of their determination of the costs of an injection. Similarly, the 80th percentile inclusion price corresponds to the price of the combination vaccine at which 80% of the population will not purchase the vaccine, for the designated number of doses. All these values are reported in Jacobson and Sewell (2002).

This analysis suggests that the combination vaccines provide good economic value. For example, if a health care provider believes that for their patient population, the cost of an injection follows a normal distribution with mean \$20 and standard deviation \$4, and this provider wishes to stock combination vaccine **DTP_a-HIB-HBV** for administration of two doses per child during the first five years of the immunization schedule, with a child already having been administered a birth dose of **HBV**, then if the price of this combination vaccine is \$36, approximately 20% of rational purchasers of vaccine for this provider’s patients would be willing to bear the cost of this combination instead of using the currently licensed vaccines. However, if the price is dropped to \$31, then approximately 80% of vaccine purchasers will be willing to bear the cost of this combination over taking the currently licensed vaccine injections. On the other hand, if the vaccine purchaser believes that the cost of an injection follows an exponential distribution with mean \$20 (hence the population has a larger coefficient of variation for their injection cost distribution), then the 20% and 80% prices are \$42 and \$28 respectively. Therefore, higher coefficients of variation tend to result in a wider variation in combination vaccine prices. This information provides health care providers with valuable practical information on how many doses of this combination should be stocked. This also provides useful formulary information for health care providers, as well as information that can benefit suppliers and insurance companies in assessing *a priori* the impact of combination vaccines on ordering and reimbursement processing, respectively. Similar results and analysis can be obtained from each of the other vaccines and distributions.

The standard deviations of the inclusion prices are positively related to the standard deviations of the injection cost distributions. For example, for the one dose formulary, the values for s corresponding to the three injection cost distributions (uniform, normal and exponential distributions with mean \$20, hence their standard deviations are \$5.77, \$4, and \$20, respectively) are \$12, \$4, and \$22, respectively. This means that for a $U[0, \$40]$ injection cost distribution, the standard deviation for the inclusion prices of **DTP_a-HBV-IPV** is \$5.77, while for an exponential distribution with injection cost mean \$20, the standard deviation for the inclusion prices of **DTP_a-HBV-IPV** is \$22. Therefore, as the injection cost distribution standard deviation increases, the inclusion price distribution also increases, though this relationship may be nonlinear (particularly for the uniform distribution) and depends on the form of the injection cost distribution. One consequence of this observation is that health care providers are more easily able to predict the volume of various combination vaccines to stock in their formularies based on the homogeneity of their assumed injection costs (which affects the economic value of the multivalent combinations) as well as the quantified willingness (to pay) of their patients to avoid injections. Moreover, vaccine manufacturers must be more sensitive to how they set the price of their combination vaccines for such populations, since small changes in their price can lead to significant changes in the volume of vaccines that they are able to sell.

The results presented in Jacobson and Sewell (2002) are based on the Federally negotiated prices for the twelve vaccines currently under contract with the CDC, hence represent the maximum Federal prices at which the four combination vaccines enter the vaccine formulary one and two or three times. These values only apply for vaccine providers eligible for publicly purchased vaccine. The higher prices of existing vaccines in the private-sector would produce correspondingly higher inclusion prices for the pentavalent and hexavalent vaccines studied. Note that for **DTP_a-HIB-IPV**, three doses rather than two doses are reported since three doses of this vaccine can be used without any extravaccination occurring. The other combination vaccines result in extravaccination occurring if administered three times.

The nine distributions for the cost of an injection analyzed for each of the six cases resulted in a total of fifty-four Monte Carlo experiments. For each Monte Carlo experiment, a histogram plot of the inclusion prices was obtained. For the normal and exponential distributions, the histogram plot shape for the inclusion prices preserves these distributions, with shifted means and variances as reported in Jacobson and Sewell (2002). However, for the uniform distributions, the histogram plots for the inclusion prices do not appear to preserve the shape of the uniform distribution (see Jacobson and Sewell 2002). Figures 1-3 provide these histogram plots for the **DTP_a-HBV-IPV** vaccine product reported in Jacobson and Sewell (2002), with injection cost distributions $U(\$0, \$40)$, $N(\$20, \$4)$,

and exponential with mean \$20, respectively. Given that the distributions are preserved for the normal and the exponential injection cost distributions suggest a possible linear relationship between the cost of an injection and the inclusion prices; this is consistent with the relationship between these injection cost distribution standard deviations and the inclusion price standard deviations. However, the result in Figure 1 suggests that this is not the case for the uniform distribution, which may be due in part to the fact that for the uniform injection cost distribution, many of the injection costs may be close to zero. Therefore, each injection cost distribution must be treated individually to determine the correct inclusion price distribution for a given combination vaccine for a particular population.

The inclusion prices reported in Jacobson and Sewell (2002) also provide valuable marketing information for vaccine manufacturers. For example, if the manufacturer of a combination vaccine would like to target their product at a particular sector of a community that places a high value on the cost of an injection (e.g., exponential with mean $\mu = \$45$), then the manufacturer can price their product accordingly and know what fraction of that sector will be willing to pay that price.

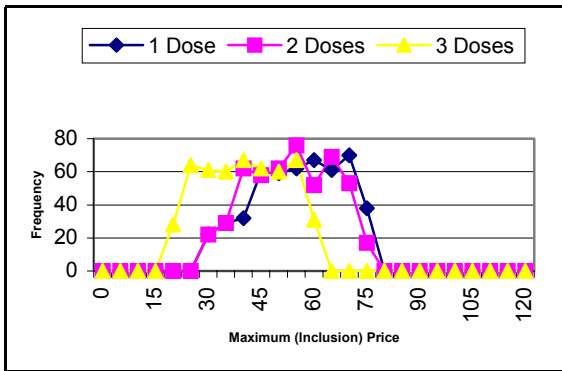


Figure 1: Inclusion (Maximal) Price Distribution for DTPa-HBV-IPV with U(0,40) Injection Cost Distribution

5 CONCLUSIONS AND LIMITATIONS OF RESULTS

This paper uses Monte Carlo simulation and integer program modeling to determine inclusion price distributions for four combination vaccines that are being developed for immunization against six childhood diseases. The results reflect the cost premiums that combination vaccines merit over separate vaccines based on the cost values (and their distribution) assigned to administering each injection. Further developments and innovations in this area by vaccine manufacturers can be driven by the resulting economic and societal benefits measured by such analyses.

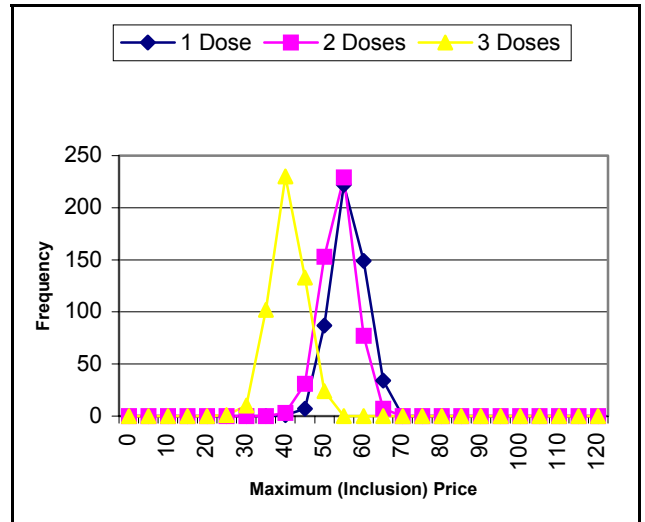


Figure 2: Inclusion (Maximal) Price Distribution for DTPa-HBV-IPV with N(20,4) Injection Cost Distribution

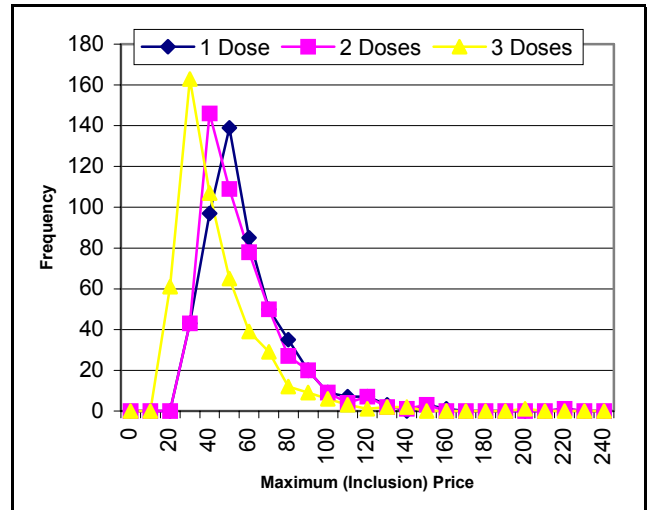


Figure 3: Inclusion (Maximal) Price Distribution for DTPa-HBV-IPV with Exp(20) Injection Cost Distribution

The inclusion price distributions given for the four combination vaccines (Jacobson and Sewell 2002) provide useful information for determining what fraction of a purchasing population would use a given pentavalent or hexavalent combination vaccine at a specified price. Note that these distributions are highly sensitive to the data described in Section 2, including the price of each vaccine, the removal or addition of any vaccine product, and the formulation and packaging (hence the preparation costs) for each vaccine product (Jacobson and Sewell 2002). Note that this study did not attempt to match each of the combination vaccines against each other, but rather looks at the effect of adding each combination vaccine individually to the currently available and licensed vaccine products. As these combination vaccines are priced in the mar-

ketplace), such a study would be appropriate and useful to help health care providers assess whether any or all such products have a place within their vaccine formulary.

Other factors stated in Section 2 that also impact the overall cost of immunization would add an additional level of realism to the results reported here. As data is collected to determine such costs, the resulting cost components can be incorporated into the integer programming model, hence provide more accurate combination vaccine inclusion price distributions. However, the costs associated with vaccine-preventable disease incidence may lead to non-linear cost functions, resulting in non-linear integer programming models. The nature of this non-linearity (e.g., convexity, multi-modal) will determine whether the approach used in this paper can be extended to handle such cost factors, or whether a new modeling approach is required.

The inclusion price distributions for the four combination vaccines are obtained based on the assumptions stated in Section 2. Note that the effect of issues such as brand loyalty and other behavioral factors were not included in the study hence the results reported do not capture such factors. In addition, the data used to obtain these distributions, such as the injection cost distributions and the cost of vaccine preparation, are highly dependent on specific factors germane to each individual health care provider or clinic, hence any changes in these data can result in changes to the inclusion price distributions for the combination vaccines. Therefore, given these limitations, the values reported in Jacobson and Sewell (2002) should serve as general guidelines, rather than precise values as to how the combination vaccines should be valued in the marketplace, since any or all of these other factors may serve to either increase or decrease such values.

As new vaccine combination products enter the market and become licensed for administration, the combinatorial explosion of choices available to health care providers will make it even more challenging to make sound economic decisions. The operations research modeling approach presented in this paper provides a systematic methodology to address such issues, hence encourages intelligent and cost effective decision-making in the rapidly expanding combination vaccine development arena. Moreover, once these combination vaccines are priced in the marketplace, healthcare providers and insurance companies can use the operations research modeling approach used in this study to assess whether such products provide a good value for their particular patient population and circumstances.

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