Journal of Mathematical Modeling
Vol. , No. , , pp. -

JMM

A multi objective model for maximizing immunogenicity level of vaccination while minimizing cost and extra-immunization

Ahmad Makui*, Rouzbeh Ghousi and Saeid Zhalefruzan

†*Department of Industrial Engineering, Iran University of Science and Technology, Tehran, Iran*

email: amakui@iust.ac.ir, ghousi@iust.ac.ir, saeidzhalefruzan@yahoo.com

Abstract. Mortality decrease due to immunizing is the achievement of vaccination. Immunizing faces challenges: Immunogenicity level, cost and extra-immunization. To overcome these a multi-objective Maximizing Immunogenicity, minimizing Cost and Extra-immunization model with Different Vaccine Formulary (ICEDVF) is introduced. Usually, Costs and budget lead to incomplete immunizing. Providing concept of immunogenicity under a fixed budget, the ICEDVF model seeks vaccines maximize immunogenicity and minimize both cost and extra immunization. The augmented e-constraint method is applied to solve ICEDVF and the results are presented for the U.S.

Keywords: Pediatric vaccination, mixed vaccines, immunogenicity, multi objective, augmented epsilon constraint.
AMS Subject Classification: 90B35, 90C06, 90C10, 90C29, 90C90.

1 Introduction

Vaccination is one of the most effective public health endeavors to decrease mortality due to infectious diseases [12, 13]. Thanks to vaccination, the risk of various diseases among children has significantly decreased and human life expectancy has increased from the age of 46 in 1950 to the age of 61 and 67 in 1980 and 1988 respectively [1].

*Corresponding author.
Received: 6 June 2017 / Accepted: 14 August 2017.
DOI: 10.22124/jmm.2018.7695.1102

The purpose of the Center for Disease Control and Prevention (CDC), as the main social health organization in the U.S., is to be in charge of providing vaccines for public health centers [8,12]. This organization introduces the Recommended Childhood Immunization Schedule (RCIS) annually based on the reports provided by the Advisory Committee on Immunization Practice (ACIP). This program includes the different doses necessary for infectious diseases and recommended time period for immunizing each dose of the disease (Figure (1)). For example, according to this schedule, four doses have been recommended for IPV disease. In such a way that the third dose has been recommended to be immunized at the age of six, twelve, fifteen, or 18 months. Another duty of the CDC is to introduce vaccines confirmed by the Food and Drug Administration (FDA) and also to determine prices for these vaccines [4]. In this research three different challenges faced by vaccinators in implementing the immunization program in different countries is studied. These challenges include immunization level, cost and extra-immunization.

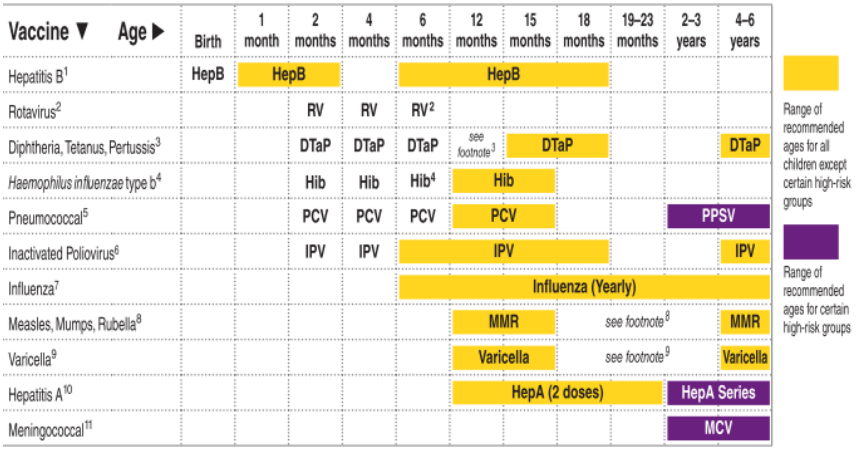

Figure 1: United States 2010 recommended childhood immunization schedule (RCIS). The horizontal bar indicates recommended time periods for immunization and the disease are depicted in vertical bar.

1.1 Immunization level challenge

Immunization policies highly depend on budget constraints of countries. For example, developed countries that don't face any budget limitations implement immunization schedule completely while developing countries are not able to implement the immunization schedule comprehensively due

to the budget limitations and are seeking to maximize the immunization level acquired in the country. In this research, by providing the concept of immunogenicity (the immunization level obtained against Type D disease, after immunizing the j^{th} dose of Type D disease) [6] maximizing the level of immunogenicity under fixed budget is sought. Moreover, by implementing our proposed model, charitable organizations will be able to perform the immunization program in poor countries under a specific budget in such a way that the maximized immunization level can be acquired. Since all the investigated vaccines in this research are confirmed by FDA, immunization can be achieved through different formulations. An immunization formulation in a given period of time, consists of a vaccine(s) so that some or all of the target diseases are immunized in the time period by antigen(s) in the vaccine(s). For instance, two different immunization formulations can be considered in order to immunize IPV, Hib, and DTaP diseases at the age of two months. The first formulation consists of Pediarix vaccine containing IPV, HIB, and DTaP antigens, and the second formulation consists of Kinirix and PedvaxHib vaccines containing IPV, DTaP, and HIB antigens, respectively.

1.2 Cost and extra-immunization challenge

Identifying new infectious diseases and seeking to discover related vaccines, the number of injections have increased, the immunization schedule has become more complicated, and vaccinators have faced the challenge of decreasing expenses and extra-immunization. For example, according to the U.S. immunization schedule in 2010, six injections were suggested in the second month which is a high number of injections in one visit to the clinic. Complication in the immunization schedule increases the probability of pediatrics not visiting health care centers thus not completing the immunization schedule leading to an increase in the risk of infectious diseases and expenses for families and society. For example, with the prevalence of measles in the U.S. in 1990, 280000 people suffered from this disease. Most of these patients hadn't had measles injections thoroughly [11]. Weniger et. al. (1996) suggested using mixed vaccines in order to simplify the immunization schedule complexity [16]. These vaccines contain multiple antigens and decrease the number of injections. For example, Pediarix vaccine which contains HepB, DTaP, and IPV antigens decreases the number of injections from 3 to 1.

By introducing mixed vaccines into the childhood immunization schedule, vaccine manufactures conducted more research on producing these vaccines and provided the market with new vaccines. By injecting mixed vac-

cines, the probability of extra-immunization increases. Extra-immunization is a state in which the number of injected doses is higher than the recommended doses by immunization schedule or immunization of a disease takes place in a different period from the recommended period by immunization schedule. For example, according to immunization schedule in 2010, Pediarix injection in 4^{th} month leads to extra-immunization of Hepatitis B. Extra-immunization can be harmful to some diseases and must be prevented. With an increasing number of mixed vaccines in the market, managers of vaccine industry encounter selecting challenges in order to minimize the costs of implementing recommended immunization and extra-immunization schedule. Minimizing these two factors are investigated in this paper.

Vaccine production needs broad and time-consuming biological researches. Therefore, the risk of entering vaccine industry is high requiring a huge amount of capital. Also, due to the increases in production costs, this industry often has low profit. Requiring huge amounts of capital and high risk on one hand, and less profitability on the other hand, have led to factory's failure [12]. For example, until 2010, there were only 6 factories in America while 3 of them produced only one type of vaccine [2]. Considering the mentioned reasons, decrease in the number of manufacturers and consequently decrease in vaccines produced is probable; therefore, there might be problems in the immunization schedule [17]. Thus, regular and accurate implementation of immunization schedule needs robust vaccine industry i.e. manufacturers must continue producing the current vaccines and doing researches on new ones. In the U.S., the federal government has signed contracts to provide financial incentives for manufacturers encouraging them to produce and conduct researches on vaccines preventing their failure and bankruptcy. As a result, having a certain profit level necessary for vaccine manufacturers is also investigated in this paper.

Researchers have used operation research methods in order to solve childhood immunization problems. Most researches have focused on determining optimum immunization policy i.e. vaccines for immunization must be selected in such a way that not only is the recommended immunization schedule satisfied but also that implementation costs of the schedule are minimized. Weniger et al suggested a linear binary model based on a recommended immunization schedule in order to determine optimized childhood immunization formulation. They analyzed different scenarios: injection of the Hepatitis B vaccine at the time of birth, injection of the first vaccine at the age of two months, and injection of the first vaccine at the age of two months in such a way that at least one vaccine is chosen from each manu-

facturer in optimum policy [16]. Jacobson et al provided more explanation on Weniger's model. They considered extra-immunization in their model for the first time, not allowing extra-immunization of infectious diseases, namely, measles, mumps, and rubella [9]. Hal et al presented a comprehensive model to decrease extra-immunization and immunization costs using dynamic programming to solve the proposed model [7]. Robins and Jacobson introduced Monopsonist Vaccine Formulary Pricing and Purchasing Problem (MVF3P) to determine the prices of manufacturers' vaccines so that manufacturers can gain a specific profit from vaccines minimizing the cost of implementing immunization schedule. Tomlab solver is used to solve their non-linear model [14]. Finally, in 2016, Robins and Landy introduced a bi-level model to maximize vaccine manufacturers' profit. They solved their model through heuristic sampling methods.

In this research, an attempt is made to investigate optimized policy of immunization in order to maximize immunization level, minimize costs and extra-immunization, through considering different immunization formulations in each period and specified profit level for different manufacturers. Multi objective Mixed Integer Nonlinear Programming (MINLP), called maximizing Immunogenicity, minimizing Cost and Extra-immunization with Different Vaccine Formulary (ICEDVF), is used in order to specify vaccines for implementing the immunization schedule under a limited budget. It also maximizes the immunization level and minimizes immunization costs and extra-immunization in the society. Nonlinear ICEDVF model can be used by governments to determine the optimum number of vaccines for implementing the immunization schedule under a fixed budget.

The paper is organized as follows: in Section 2, an MINLP model is presented to optimize ICEDVF for determining the number of purchased vaccines in different periods under a given budget in order to implement recommended immunization schedule and ascertain profit for different manufacturers. In Section 3, linearizing method and augmented epsilon constrained are provided. Section 4 provides the results of applying ICEDVF for the U.S. recommended immunization schedule; optimum amounts of vaccines under a given budget for implementing recommended immunization schedule are presented. Section 5 provides the conclusion and further recommendations.

2 Model formulation

In this section, an MINLP model is presented to optimize ICEDCF in order to determine optimum policies of the vaccines used in each formulation of

the period and the number of formulations for implementing the immunization schedule under a given budget ascertaining a profit for different manufacturers. Cost parameters used in the ICEDCF model include vaccines price, preparation cost, and injection cost. The amount of vaccines in each formulation in each period and the number of each formulation must minimize the cost of immunization implementation and the number of extra-immunizations. Also, vaccines must be selected so that the minimum immunization level determined by the decision maker is satisfied for all diseases. Sets and parameters definitions required to describe the ICEDCF model are as follows:

$T = \{1, 2, \cdots, \tau\}$	set of periods in Recommended childhood immunization Schedule
$D = \{1, 2, \cdots, \delta\}$	set of disease in Recommended childhood immunization Schedule
$M = \{1, 2, \cdots, \mu\}$	set of vaccine manufactures
$V = \{1, 2, \cdots, \nu\}$	set of available vaccines
P_v	price of vaccine $v \in V$
PP_v	preparation cost of vaccine $v \in V$
IC	Injection cost
C_v	production cost of vaccine C
n_d	number of recommended doses for disease $d \in D$
α_{dj}	j^{th} doses immunogenicity for disease $d \in D,\ j = \{1, 2, \cdots, n_d\}$
θ	Minimum immunogenicity for each disease
B_m	profit of manufacture $m \in M$
F_t	Number of immunization formulation at $t \in T,\ f = \{1, 2, \cdots, F_t\}$
β	allocated budget for immunization
pop	Population that must be immunized
Ψ	Adequate big number
I_{vd}	1 if vaccine $v \in V$ contains antigen disease $d \in D$; 0 otherwise
S_{djt}	1 if j^{th}, $j = \{1, 2, \cdots, n_d\}$ doses of $d \in D$ can be immunized at period $t \in T$; 0 otherwise
Z_{vm}	1 if vaccine $v \in V$ produced with manufacture $m \in M$; 0 otherwise
π_{dj}	1 if j^{th}, $j = \{1, 2, \cdots, n_d\}$ doses of $d \in D$ immunized; 0 otherwise
η_{dj}	1 if j^{th}, $j = \{1, 2, \cdots, n_d\}$ doses of $d \in D$ immunized at period $t \in T$; 0 otherwise
X_{vft}	1 if formulation $f = \{1, 2, \cdots, F_t\}$ contains vaccine $v \in V$ at period $t \in T$; 0 otherwise
ξ_t	1 if any immunization occurred at period $t \in T$; 0 otherwise
Y_{ft}	Number of people immunized with formulation $f = \{1, 2, \cdots, F_t\}$ at period $t \in T$.

ICEDVF MODEL

$$\max \sum_{d \in D} \sum_{j=1}^{n_d} \alpha_{dj} \times \pi_{dj} \tag{1}$$

$$\min \sum_{v \in V} \sum_{t \in T} \sum_{f=1}^{F_t} X_{vft} \times Y_{ft} \times (P_v + PP_v + IC) \tag{2}$$

$$\min \sum_{d \in D} \left(\sum_{t \in T} \left(\sum_{v \in V} \sum_{f=1}^{F_t} X_{vft} \times Y_{ft} \times I_{vd} - \sum_{j=1}^{n_d} \eta_{djt} \times POP \right) \right) \tag{3}$$

$$\pi_{dj} = \sum_{t \in T} \eta_{djt} \times S_{djt}, \qquad \forall d \in D,\ \forall j \in n_d, \tag{4}$$

$$\sum_{j=1}^{n_d} \alpha_{dj} \times \pi_{dj} \geq \theta, \qquad \forall d \in D, \tag{5}$$

$$\sum_{v \in V} X_{vft} \times I_{vd} \times S_{djt} \geq \eta_{djt}, \qquad \forall d \in D,\ \forall j \in n_d,\ \forall t \in T,\ \forall f \in F_t, \tag{6}$$

$$\sum_{d \in D} \sum_{j=1}^{n_d} \eta_{djt} \leq \psi \times \zeta_t, \qquad \forall t \in T, \tag{7}$$

$$\sum_{d \in D} \sum_{j=1}^{n_d} \psi_{djt} \geq \zeta_t, \qquad \forall t \in T, \tag{8}$$

$$\sum_{f=1}^{F_t} Y_{ft} = \zeta_t \times pop, \qquad \forall t \in T, \tag{9}$$

$$\sum_{t \in T} \sum_{f=1}^{F_t} \sum_{v \in V} X_{vft} \times Z_{vm} \times Y_{ft} \times (P_v - C_v) \geq B_m, \qquad \forall m \in M, \tag{10}$$

$$\sum_{t \in T} \sum_{v \in V} \sum_{f=1}^{F_t} X_{vft} \times Y_{y,f_t} \times P_v \leq \beta, \tag{11}$$

$$\pi_{dj}(j+1) \leq \pi_{dj}, \qquad \forall d \in D,\ \forall j \in n_d. \tag{12}$$

Objective function (1) aims to maximize obtained immunization level in society using immunogenicity level obtained through injecting different doses of one disease (α_{dj}). Objective function (2) minimizes immunization costs considering the number of users of each formulation and vaccines contained in each one. Finally, objective function (3) minimizes extra-immunization resulting from implementing the immunization schedule (since extra-immunization is harmful and must be prevented as much as possible). Based on the minimum level of immunization for each disease, constraints (4) and (5) determine the period of immunizing j^{th} doses of disease d. Constraint (6) determines vaccine(s) of formulations in each period which contain antigen(s) of the immunized disease(s) in the period. Constraints (7) and (8) determine the periods in which immunization has happened. Constraint (9) determines the number of immunized people through different immunization formulations in each period in a way that the whole population is covered. Constraint (10) guarantees the specified profit for manufacturers. Constraint (11) ensures that the whole purchased vaccine price is less than the considered budget. Finally constraint (12) ensures that the j^{th} dose of disease d can only be immunized if the j-1th

dose was immunized.

3 Linearization of ICEDVF

The proposed model for optimizing ICEDCF problem in the second section is nonlinear in which the nonlinear factor is the multiplication of the binary variable by the continues variable. The model is linearized through Glover's method introduced in 1975 [5]. For example, for linearizing $X \times Z$ in which X is a binary and Z is a continues variable, $X \times Z$ is substituted by Y and the three constraints below are added to the model (M is the upper bound of variable Z):

$$y \leq M \times x, \tag{13}$$
$$y \geq z + M \times x - M, \tag{14}$$
$$y \leq z. \tag{15}$$

In ICEDCF, nonlinear factor $X_{vft} \times Y_{ft}$ in equations (2), (3),(10) and (11) is substituted by new variable δ_{vft} and three constraints are added to the model. Also, the population covered by immunization schedule (POP) is considered as the upper bound of the continues variable (Y_{ft}):

$$\delta_{vft} \leq POP \times X_{vft}, \qquad \forall(v \in V,\ t \in T,\ f \in F_t), \tag{16}$$
$$\delta_{vft} \geq Y_{ft} + POP \times X_{vft} - POP, \quad \forall(v \in V,\ t \in T,\ f \in F_t), \tag{17}$$
$$\delta_{vft} \leq Y_{ft}, \qquad \forall(v \in V,\ t \in T,\ f \in F_t). \tag{18}$$

3.1 Solving methodology

In order to solve multi-objective ICEDCF and provide Pareto optimal solutions, augmented e-constraint which was introduced by Mavrotas is used [10]. We assume that the multi-objective optimization problem can be expressed as equation (19):

$$\begin{aligned} &\max \ \ (f_1(x), f_2(x), \cdots, f_p(x)) \\ &st: \ X \in S. \end{aligned} \tag{19}$$

In this method, one of the objective functions is considered as the main objective function and other functions are considered as constraints. Thus, the problem can be rewritten by equation (20) as single-objective problem. (eps: a number which is small enough, r_i: the obtained limits for i^{th}

objective function from Payoff Table 1):

$$\begin{aligned} \max \left(f_1(x) + eps \times \left(\frac{s_2}{r_2} + \frac{s_3}{r_3} + \cdots + \frac{s_p}{r_p} \right) \right), \\ f_2(x) - s_2 = e_2, \\ f_3(x) - s_3 = e_3, \\ \vdots \\ f_p(x) - s_p = e_p, \qquad x \in S \ \text{ and } \ s_i \in \mathbb{R}^+. \end{aligned} \tag{20}$$

By changing the right-hand side values of the objective functions which were considered as constraints $(e_2, e_3, \ldots, e_p)$ and solving the model (20), Pareto optimal solutions can be obtained. Mavrotas used payoff Table 1 to determine the values of the right-hand side of the objective functions considered as constraints. The values in this table were calculated through Lexicographic optimization.

Table 1: Payoff table obtained by the lexicographic optimization of the objective functions

Max / OBJ	OBJ_2	OBJ_3	$\cdots$	OBJ_p
OBJ_2	$F_{2,2}$	$F_{3,2}$	$\cdots$	$F_{p,2}$
OBJ_3	$F_{2,3}$	$F_{3,3}$	$\cdots$	$F_{p,3}$
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
OBJ_p	$F_{2,p}$	$F_{3,p}$	$\cdots$	$F_{p,p}$

In Table 1, F_{ii} is the optimal value of i^{th} objective obtained based on model (21), $i \in \{2, 3, \cdots, p\}$.

$$\begin{aligned} \max \ & f_i(x) \\ s.t: \ & x \in S. \end{aligned} \tag{21}$$

In Table 1, F_{ij} is the optimal value of i^{th} objective obtained based on model (22), $i, j \in \{2, 3, \cdots, p\} (i \neq j)$.

$$\begin{aligned} \max \ & f_i(x) \\ s.t: \ & f_i \geq F_{j,j}, \\ & f_i \geq F_{i,j}, \qquad \forall i \in \{2, 3, \cdots, i-1\} \text{ and } i \neq j, \\ & x \in S. \end{aligned} \tag{22}$$

After calculating F_{ij} and F_{ii}, the bounds of the objective functions considered as constraints are calculated according to equation (23).

$$\begin{aligned} r_2 =& F_{2,2} - \min\{F_{2,3}, F_{2,4}, \cdots, F_{2,p}\}, \\ r_3 =& F_{3,3} - \min\{F_{3,2}, F_{3,4}, \cdots, F_{3,p}\}, \\ & \vdots \\ r_p =& F_{p,p} - \min\{F_{p,2}, F_{p,3}, \cdots, F_{p,p-1}\}. \end{aligned} \tag{23}$$

Dividing r_i by q_i results in $q_i + 1$ greed points, called e_i for each objective function. Therefore, Pareto optimal solutions are obtained by solving $[(q_2+1) \times (q_3+1) \cdots \times (q_p+1)]$ problems in the model proposed in (20).

4 Computational results

This chapter provides the computational results of the MINLP ICEDCF model. Two different policies are provided for implementing the immunization schedule in the U.S. based on the recommended immunization schedule in Figure 1. The first scenario is fulfilling the immunization schedule without budget limitation, and the second scenario is immunizing with a limited budget. In both scenarios, at most two different immunization formulations are considered for each period. This section is organized as follows: Section 4.1 determines the parameters in the ICEDCF model. Sections 4.2 and 4.3 determine scenarios 1 and 2, respectively. Section 4.4 presents a discussion of the general results.

4.1 Specification of ICEDCF model parameters

Generally, the parameters used in the ICEDCF model can be organized into two categories. Parameters that have exact values include: the disease that must be immunized, time sequence and the number of doses needed for each disease based on RCIS, FDA-confirmed vaccines and their prices, and the covered population. Parameters that are difficult to evaluate accurately and need to be estimated include: immunogenicity level of each dose of each disease, production cost of one unit of different vaccines, preparation costs, and injection cost.

In this paper, based on ACIP reports in 2010, six time periods (birth, second month, fourth month, sixth month, twelfth to eighteenth month, and fourth to sixth year) and four competitive antigens (antigens whose production is not exclusive and are produced by more than one factory) are considered for ICEDCF model. These antigens include: diphtheria,

tetanus, and pertussis (DTaP), Haemophilus inuenzae type b (Hib), hepatitis B (HepB), and polio (IPV) [2].

The vaccines considered in this paper are confirmed by FDA [4]. All the necessary information for vaccines and their manufacturers are provided in Table 2. Column (1) shows the vaccine manufactures investigated in this paper [2, 4]. Antigens of each vaccine are listed in column (2) [2, 4]. Column (3) provides brand names of Pediatric vaccines. Column (4) shows the production cost of each dose of the vaccine [3]. Column (5) provides information on preparation cost of each dose of the vaccine based on vaccine type [3]. Column 6 presents selling price of each vaccine dose [2]. Injection cost of each dose is considered \$6.72 according to [15]. Also, the number of infants to be immunized according to RCIS provided by CDC is 2.3 million [14]. The considered profit for each manufacturer is calculated based on their collaboration in the vaccine market (Table 3). The annual profit of the immunization industry is considered \$400 million [14].

Table 2: necessary Vaccine data for ICEDCF Model

(1) Manufacture	(2) Antigens	(3) Vaccine	(4) Prod.cost($)	(5) Prep.cost($)	(6) Price($)
GlaxoSmithKline	DTaP	Infanrix	3.55	0.25	14.25
	Hib	Hiberix	1.45	0.75	8.66
	HepB	Engerix B	1.45	0.25	10.25
	DTaP-IPV	Kinirix	4.6	0.25	48
	DTaP-HepB-IPV	Pediarix	5.65	0.25	70.72
Merck	Hib	PedvaxHib	1.45	0.75	22.77
	HepB	Recombivax HB	1.45	0.75	10.25
	Hib-HepB	Comvax	2.5	0.75	43.56
Sanofi Pasteur	DTaP	Tripedia	3.55	0.75	14.25
	Hib	ActHIB	1.45	0.75	8.83
	IPV	IPOL	1.45	0.25	11.74
	DTaP-Hib	TriHIBit	4.6	0.75	46.346
	DTaP-Hib-IPV	Pentacel	5.65	0.75	75.33

Table 3: considered profit for each vaccine manufacture

Manufacturer	Participation (%)	Profit ($)
GlaxoSmithKline	46.00%	$184M$
Merck	13.90%	$56M$
Sanofi Pasteur	40.10%	$160M$

Table 4 provides assumed values of Immunogenicity for each dose of antigens.

At most two different immunization formulations in each period are considered for two defined policies. Computational results are obtained

Table 4: Assumed immunogenicity level for the doses of each antigens

	Dose1	Dose2	Dose3	Dose4	Dose5
DTaP	0.1	0.15	0.3	0.4	0.05
Hib	0.1	0.3	0.6		
HepB	0.35	0.45	0.2		
IPV	0.4	0.45	0.1	0.05	

using Cplex solver.

4.2 ICEDCF model without budget constraint

Considering there is no budget constraint in this policy, the lowest level of immunization for each disease (θ) is equal to 1 i.e. immunization schedule is implemented completely. With this assumption, the value of the first objective function (equation (1)) has the highest value of 4. The existing vaccines in each formulation and the number of immunized people with each formulation are provided in Table 5. According to Table 5, the cost of complete immunization is $695 million.

Table 5: summary of immunizing under no budget constraint

Vaccine	Birth		Month 2		Month 4		Month 6		Month 12-18		Year 4-6	
	F1	F2	F1	F2	F1	F2	F1	F2	F1	F2	F1	F2
Infanrix												
Pediarix												
Recombivax HB												
Comvax												
ActHIB												
IPOL												
Pentacel												
quantities	2300000		2111153	188847	1753055	546945	1228661	1071339	2300000		2300000	
Sum of Formulations	2300000		2300000		2300000		2300000		2300000		2300000	

Complete Immunization with one formulation in each period leads to an increase in costs to $52 million (%7.5). Complete immunization schedule for different populations covered by the same and different formulations are presented in Figure 2. Figure 2 shows that the complete immunizing cost with different formulations is less than the cost of immunizing with the same formulation.

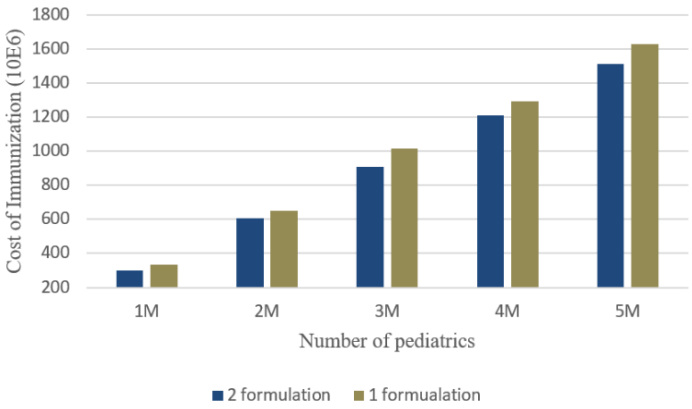

Figure 2: cost of complete immunization with the same and different formulations.

4.3 The ICEDCF model with budget constraint

Developing countries which mainly import vaccines and face budget constraints seek to maximize society immunization level with a fixed budget. Thus, the policy of incomplete immunization is appropriate for these countries. In policy of ICEDCF with budget constraint, the profit is not considered for different manufacturers (omitting equation (10)). Pareto Optimal solutions of objectives are provided in Table 6 assuming the lowest immunization level (α) of 0.5 for each disease and budget of \$400 million, which is considered only for purchasing the vaccines.

Table 6: Pareto optimal solutions of ICEDCF with budget constraint

	Objective 1 (Max)	Objective 2 (Min)	Objective 3 (Min)
1	3.2	425385000	0
2	3.6	474743000	0
3	3.8	514119000	0
4	3.9	557313000	0
5	3.95	601266000	0

The results based on fifth line of Table 6 are provided in Table 7. According to the results of the fifth line in Table 6 and Table 7, the fifth dose of DTaP disease is not immunized. Therefore, the immunization level of the society has decreased to 3.95.

Figure 3 provides the immunization level obtained in the society with assumed population of 2.3 million infants under different limited budgets. The results show that as budget increases the immunogenicity level also

Table 7:

Vaccine	Birth	Month 2	Month 4	Month 6	Month 12-18	Year 4-6
Infanrix		2300000	2300000	2300000		
Hiberix		2300000	2300000			
Engerix	2300000	2300000		2300000		
Tripedia					2300000	
ActHIB					2300000	
IPOL		2300000	2300000		2300000	2300000

increases and the complete immunization schedule will be possible with a budget of $425 million.

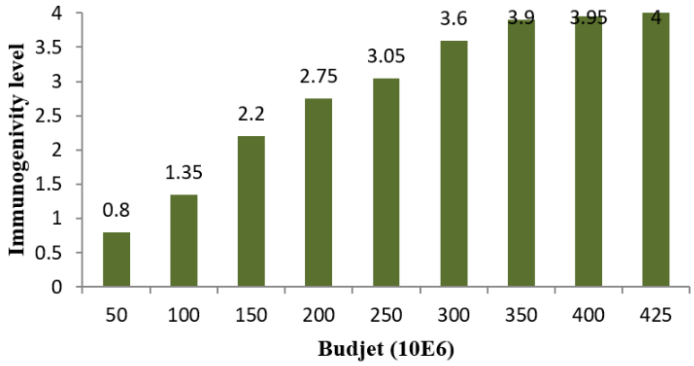

Figure 3: The immunoginicity level under dierent budget

4.4 Discussion

ICEDCF mode is a mathematical framework that specifies optimal policies of childhood vaccination for the countries not facing any budget constraints. The obtained results from ICEDCF model for this policy shows that using different formulations of immunization leads to reduction of vaccination costs. Also, ICEDCF model with budget constraint is appropriate for developing countries which don't have the ability to implement immunization schedule completely and optimum policies are described using immunogenicity concept.

5 Conclusion and research extensions

In this paper, the multi objective ICEDCF model is presented for determining optimal immunization policies. This model seeks vaccines which

not only implement the ACIP-recommended immunization schedule, but also increase immunization level obtained in the society with the lowest cost and extra-immunization. ICEDEF model is an MINLP model which is linearized using linearization techniques. In order to provide optimal Pareto solutions, the augmented e-constraint method is used.

Two different policies are considered in order to specify the optimal immunization schedule. The first policy is complete implementation of the immunization schedule, and the second policy is the incomplete implementation of the immunization schedule. The first policy seeks vaccines to implement the complete recommended childhood immunization schedule considering different immunization formulations and an appropriate profit level for manufacturers, while keeping the immunization cost minimum, the second policy seeks to maximize the immunization level in the society under a given budget. The first policy is appropriate for developed countries which don't face any budget constraint; whereas, the second policy is appropriate for developing countries and also charitable organizations that are trying to implement the immunization schedule in some poor areas. In addition to cost parameters studied in this paper, applying other parameters such as maintenance cost, wastage cost, etc. in future researches can be effective in determining the immunization schedule policy. Vials' substances lose their immunization property, shortly after opening the vials. Researchers can consider the interval arrival time of pediatrics to health centers and vials size to minimize the storage cost of vaccines.

References

[1] M.L. Brandeau, F. Sainfort and W.P. Pierskalla, *Operations research and health care: a handbook of methods and applications*, Springer Science & Business Media, 2004.

[2] Centers for disease control and prevention. Vaccine price list (contract ending 31 March 2011). Available at *http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htmS*; 2010.

[3] R.G Douglas, J. Sadoff and V. Samant, *The vaccine industry*, 5th ed. Saunders; 2008, Chapter 3.

[4] Food and Drug Administration. *Vaccines licensed for immunization and distribution in the United States*, Available at http://www.fda.gov/cber/vaccine/licvacc.htmS; 2010 [accessed 6.04.10].

[5] F. Glover, *Improved linear integer programming formulations of nonlinear integer problems*, Manage. Sci. **22** (1975) 455-460.

[6] S.N. Hall, E.C. Sewell and S.H. Jacobson, *Maximizing the effectiveness of a pediatric vaccine formulary while prohibiting extraimmunization*, Health Care Manag. Sci. **11** (2008) 339-352.

[7] S.N. Hall, S.H. Jacobson and E.C. Sewell, *An analysis of pediatric vaccine formulary selection problems*, Oper. Res. **56** (2008) 1348-1365.

[8] A.R. Hinman,*Financing vaccines in the 21st century: Recommendations from the national vaccine advisory committee*, Am. J. Prev. Med. **29** (2005) 71-75.

[9] S.H. Jacobson, T. Karnani and E.C. Sewell, *Assessing the impact of wastage on pediatric vaccine immunization formulary costs using a vaccine selection algorithm*, Vaccine. **22** (2004) 2307-2315.

[10] G. Mavrotas, *Effective implementation of the ϵ-constraint method in Multi-Objective Mathematical Programming problems*, Appl. Math. Comput. **213** (2009) 455-465.

[11] I.R. Mackay, F.S. Rosen and G. Ada, *Vaccines and Vaccination*, N. Engl. J. Med. **345** (2001) 1042-1053.

[12] W.A. Orenstein, R.G. Douglas, L.E. Rodewald, A.R. Hinman, *Immunizations in the United States: success*, structure, and stress., Health Aff. (Millwood). **24** (2005) 599-610.

[13] S.A. Plotkin, Susan L, *A short history of vaccination*, Saunders Philadelphia, 2004.

[14] M.J. Robbins and S.H. Jacobson, *Pediatric vaccine procurement policy: The monopsonist's problem*, Omega. 39 (2011) 589-597.

[15] M.J. Robbins and B.J. Lunday, *A bilevel formulation of the pediatric vaccine pricing problem*, Eur. J. Oper. Res. **248** (2016) 634-645.

[16] B. Weniger, *Addressing the challenges to immunization practice with an economic algorithm for vaccine selection*, Vaccine. **16** (1998) 1885-1897.

[17] H. Yu, A.Z. Zeng and L. Zhao, *Single or dual sourcing: decision-making in the presence of supply chain disruption risks*, Omega. **37** (2009) 788-800.