A Discrete Optimization Formulation and Analysis for the General Minimum Cost Vaccine Formulary Selection Problem[1,2,3]

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1 Joint work with Shane N. Hall and Edward C. Sewell

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3 This research was featured in *SIAM NEWS*, November 2008, pages 1,4.

Impact of Vaccines

World Health Organization (WHO): immunization and clean water have had the greatest impact on world health

Healthcare Profession: worldwide eradication of smallpox is one of the greatest achievements in public health

United States Life Expectancy (at birth):

47 years in 1900

76 years in 2003

Prevent ~3,000,000 worldwide deaths in children / year

Problem Background

Centers for Disease Control and Prevention (CDC)

- Ensures the availability of vaccines
- Monitors vaccination coverage levels
- Annually publishes the Recommended Childhood Immunization Schedule (since 1995)
  - Outlines vaccination requirements for all children living in the United States
    - * Includes number of doses for each disease
    - * Recommended age for each dose

Recommended Childhood Immunization Schedules

United States, January 1995

<table>
<tr><th rowspan="2">DISEASE</th><th colspan="8">TIME PERIOD (Age of Child)</th></tr>
<tr><th>1
(Birth)</th><th>2
(2 Mos)</th><th>3
(4 Mos)</th><th>4
(6 Mos)</th><th>5
(12 Mos)</th><th>6
(15 Mos)</th><th>7
(18 Mos)</th><th>8
(4-6 Yrs)</th></tr>
<tr><td rowspan="2">Hepatitis B</td><td colspan="2">Dose 1</td><td></td><td colspan="4">Dose 3</td><td></td></tr>
<tr><td></td><td colspan="2">Dose 2</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Diphtheria, Tetanus, Pertussis</td><td></td><td>Dose 1</td><td>Dose 2</td><td>Dose 3</td><td colspan="3">Dose 4</td><td>Dose 5</td></tr>
<tr><td>Haemophilus influenzae type b</td><td></td><td>Dose 1</td><td>Dose 2</td><td>Dose 3</td><td colspan="3">Dose 4</td><td></td></tr>
<tr><td>Polio</td><td></td><td>Dose 1</td><td>Dose 2</td><td colspan="4">Dose 3</td><td>Dose 4</td></tr>
<tr><td>Measles, Mumps, Rubella</td><td></td><td></td><td></td><td></td><td colspan="2">Dose 1</td><td></td><td>Dose 2</td></tr>
</table>

United States, January 2009

<table>
<tr><th rowspan="2">DISEASE</th><th colspan="10">TIME PERIOD (Age of Child)</th></tr>
<tr><th>1
(Birth)</th><th>2
(1 Mo)</th><th>3
(2 Mos)</th><th>4
(4 Mos)</th><th>5
(6 Mos)</th><th>6
(12 Mos)</th><th>7
(15 Mos)</th><th>8
(18 Mos)</th><th>9
(24 Mos)</th><th>10
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<tr><td>Varicella</td><td></td><td></td><td></td><td></td><td></td><td colspan="3">Dose 1</td><td></td><td></td></tr>
<tr><td>Pneumococcus</td><td></td><td></td><td>Dose 1</td><td>Dose 2</td><td>Dose 3</td><td colspan="2">Dose 4</td><td></td><td></td><td></td></tr>
<tr><td>Influenza</td><td></td><td></td><td></td><td></td><td colspan="6">Dose 1 (yearly)</td></tr>
<tr><td>Hepatitis A</td><td></td><td></td><td></td><td></td><td></td><td>Dose 1</td><td></td><td>Dose 2</td><td></td><td></td></tr>
</table>

Key Immunization Schedule Changes

Add/merge Time Periods

United States, January 2009

DISEASE	TIME PERIOD (Age of Child)									
	1 (Birth)	**2** (1 Mo)	**3** (2 Mos)	**4** (4 Mos)	**5** (6 Mos)	**6** (12 Mos)	**7** (15 Mos)	**8** (18 Mos)	**9** (24 Mos)	**10** (4-6 Yrs)
Hepatitis B	Dose 1	Dose 2			Dose 3					
Diphtheria, Tetanus, Pertussis			Dose 1	Dose 2	Dose 3		Dose 4			Dose 5
***Haemophilus influenzae* type b**			Dose 1	Dose 2	Dose 3	Dose 4				
Polio			Dose 1	Dose 2	Dose 3					Dose 4
Measles, Mumps, Rubella				[illegible]	[illegible]	Dose 1				Dose 2
Varicella				[illegible]	[illegible]	[illegible]	1			
Pneumococcus			Dose 1	[illegible]	[illegible]	[illegible]	[illegible]			
Influenza				[illegible]	[illegible]	[illegible]	se 1 (yearly)			
Hepatitis A				[illegible]	[illegible]	[illegible]	[illegible]	Dose 2		

Change in Vaccine Policy

-Dose Requirements

-New biotechnology

-Advancing medical knowledge

Add/remove Diseases

-Eradication

-Emerging/reemerging infectious disease

Combination Vaccines

- Two-month well-baby checkup

1995 Vaccines

HBV
DTP
HIB
OPV

DISEASE	Time Period 3 (2 Mos)
Hepatitis B	Dose 2
Diphtheria, Tetanus, Pertussis	Dose 1
***Haemophilus influenzae* type b**	Dose 1
Polio	Dose 1
Pneumococcus	Dose 1

2009 Vaccines

HBV
DTaP
HIB
IPV
PNU

HBV-HIB
DTaP-HIB
DTaP-HBV-IPV
DTaP-HIB-IPV

Vaccination Options in 1995:

1. HBV, DTP, HIB, OPV

Vaccination Options in 2009:

1. HBV, DTaP, HIB, IPV, PNU
2. HBV, DTaP-HIB, IPV, PNU
3. HBV-HIB, DTaP, IPV, PNU
4. DTaP-HBV-IPV, HIB, PNU
5. DTaP-HIB-IPV, HBV, PNU
6. HBV-HIB, DTaP-HIB, IPV, PNU
7. HBV-HIB, DTaP-HBV-IPV, PNU
8. HBV-HIB, DTaP-HIB-IPV, PNU
9. DTaP-HIB, DTaP-HBV-IPV, PNU
10. DTaP-HBV-IPV, DTaP-HIB-IPV, PNU

⇒ A combinatorial explosion of immunization alternatives

Problem Statement

- What is the optimal vaccine formulary?
  - Vaccine formulary: the inventory of vaccines a pediatrician or clinic maintains in order to satisfy the Recommended Childhood Immunization Schedule (RCIS)
- Determine the minimum cost way to satisfy the RCIS
  - Vaccine formulary comprises the vaccines administered in the optimal solution

Solution Methodologies

- Optimization Problem
  - General Minimum Cost Vaccine Formulary Selection Problem (GMCVFSP)
- Modeling Approaches and Algorithms
  - Exact Methods: IP and DP
  - Heuristics: intuitive constructive heuristics

Literature Review

- Weniger et al. (1998) & Jacobson et al. (1999)
  - Collaborative pilot study between CDC/academia
    - Modeled sub-schedule as integer program (IP)
  - Optimal vaccine formularies based on differing economic criteria
- Sewell et al. (2001) & Sewell and Jacobson (2003)
  - IP combined with bisection algorithm to "reverse engineer" maximum inclusion prices of potential combination vaccines
  - Jacobson et al. (2003b)
    - Demonstrates this analysis for Hepatitis B-*Haemophilus* influenzae type b combination vaccine
- Jacobson and Sewell (2003)
  - IP/bisection algorithm combined with Monte Carlo simulation
    - Sampled different injection costs to determine probability distribution for price of combination vaccines

Visit https://netfiles.uiuc.edu/shj/www/shj.html for a complete list of papers.

Model Preliminaries

Given an arbitrary CIS:

- SETS: Time Periods, $T = \{1,2,\ldots,\tau\}$, $t \in T$, Diseases, $D = \{1,2,\ldots,\delta\}$, $d \in D$, Vaccines, $V = \{1,2,\ldots,\upsilon\}$, $v \in V$
- INTEGER PARAMETERS:
  - n_d (dose requirement for disease $d \in D$), $j = 1,2,\ldots,n_d$
  - m_{dt} (minimum # of doses required for disease $d \in D$ through time period $t \in T$)
  - M_{dt} (maximum # of doses required for disease $d \in D$ through time period $t \in T$)
  - c_v (cost of vaccine $v \in V$)
- BINARY PARAMETERS: Schedule Indicators and Vaccine Indicators

$$P_{djt} = \begin{cases} 1 & \text{if dose requirement } j \text{ for disease } d \in D \text{ may be satisfied in time period } t \in T \\ 0 & \text{otherwise} \end{cases}$$

$$I_{vd} = \begin{cases} 1 & \text{if vaccine } v \in V \text{ immunizes against disease } d \in D \\ 0 & \text{otherwise} \end{cases}$$

Model Preliminaries (Cont.)

- DECISION VARIABLES:

$$X_{tv} = \begin{cases} 1 & \text{if vaccine } v \in V \text{ is administered in time period } t \in T \\ 0 & \text{otherwise} \end{cases}$$

$$U_{dt} = \text{\# of required vaccine doses administered for disease } d \in D \text{ through time period } t \in T$$

- OBJECTIVE: Minimize the cost of vaccines
- CONSTRAINTS: Satisfy CIS
  - Every dose requirement (in the appropriate time window) is satisfied by at least one vaccine
  - Assumes *extraimmunization* is allowed

Cost and Extraimmunization

What is the cost of a vaccine?

- Monetary cost of vaccine
  - Federally negotiated contract prices vs. commercial prices
- Preparation and storage
- Cost of an injection
- Parental/guardian opportunity costs

Extraimmunization

- If less costly, it should be allowed
- Extra vaccine doses (in most cases) are biologically safe
- Combination vaccines have been designed to limit extraimmunization
  - This recently changed with the FDA approval of Pentacel©
- Cost objective naturally discourages extraimmunization

GMCVFSP IP

Integer Programming (IP) Model

Minimize $\sum_{t \in T} \sum_{v \in V} c_v X_{tv}$

Subject to

$$U_{dt} \le U_{d(t-1)} + 1 \qquad \forall\, d \in D, t \in T$$

$$U_{dt} \le U_{d(t-1)} + \sum_{v \in V} I_{vd} X_{tv} \qquad \forall\, d \in D, t \in T$$

$$m_{dt} \le U_{dt} \le M_{dt} \qquad \forall\, d \in D, t \in T$$

$$X_{tv} \in \{0,1\} \qquad \forall\, t \in T, v \in V$$

$$U_{dt} \text{ integer} \qquad \forall\, d \in D, t \in T$$

Computational Complexity

- *GMCVFSP* is *NP-hard*
  - follows directly from Set Covering
- Remains *NP*-hard when
  - $\tau = 1$, $c_v = 1$ for all $v \in V$, and $n_d = 1$ for all $d \in D$
  - Only one vaccine exists in V
  - $\delta \geq 3$
  - Every vaccine is at least trivalent
- Polynomial Special Cases
  - Monovalent vaccines
  - Bivalent Vaccines
  - $\delta \leq 2$
  - *Tight* CIS (i.e., a single time window for each dose)

GMCVFSP DP

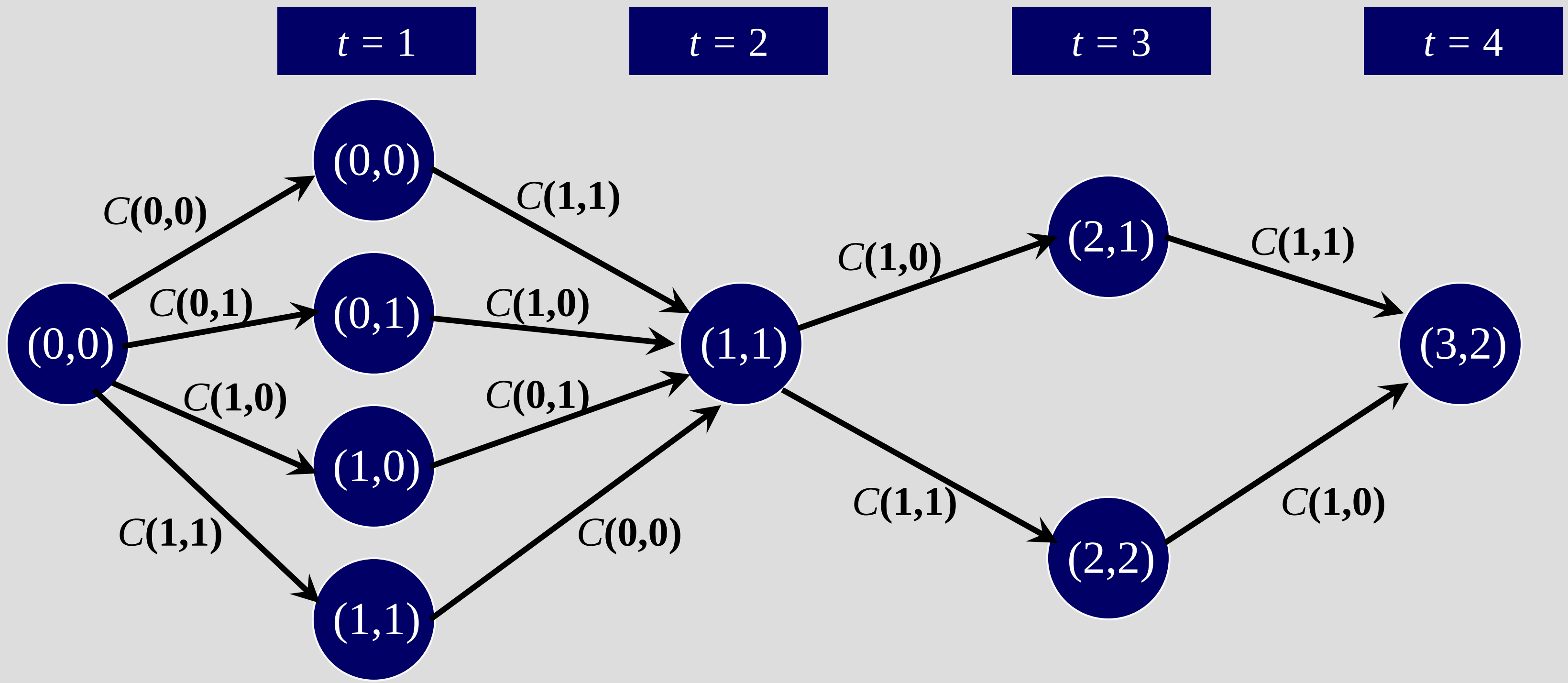
- Dynamic Programming (DP) approach
  - “Divide and Conquer” technique
    - Divide problem into several sub-problems
    - Sub-problems are *not* independent
- Solves GMCVFSP, one time period at a time
  - Begins with first time period and moves forward in time
- DP offers several advantages
  - Efficient in practice
  - Provides realistic and theoretical decomposition
  - Robust optimization framework

GMCVFSP DP

- Can be viewed as a shortest path network flow problem
- U_{dt} decision variables characterize the *states* (nodes in the network)
- X_{tv} decision variables characterize the *decisions* (arcs in the network)

GMCVFSP DP

DISEASE	TIME PERIOD			
	1	**2**	**3**	**4**
1	Dose 1		Dose 2	Dose 3
2	Dose 1		Dose 2	



(C) Jacobson

GMCVFSP DP

- Executes in $O(\tau(\mathbf{S}_{MAX})^2\mathbf{T}_{SCP})$ time, where
  - $\mathbf{S}_{MAX}$ *is the* maximum # of states in any time period
  - $O(\mathbf{T}_{SCP})$ is the time to solve the set cover problem at each time period
  - τ is the number of time periods
- Using "branch and remember" recursive algorithm, DP executes in $O(\tau\delta(\mathbf{S}_{MAX})^2 + \upsilon\delta 2^{\delta})$ time

Heuristics & Approximation Algorithms

- Assume every disease $d \in D$ has *mutually exclusive doses* (i.e., nonoverlapping dose time periods)
  - Simplifies optimization models
    - Constraints involving U_{dt} variables become redundant
  - Practical assumption
    - Every disease $d \in D$ in the current (2008) Recommended Childhood Immunization Schedule has *mutually exclusive doses*
- Define $\mathbf{T}_{LP}$ as the time needed to solve the LP relaxation of the respective optimization problem
- $D = \Sigma_{d=1,2,\ldots,\delta}\, n_d$, the total number of doses to be administered.

MAX Rounding Heuristic

- Rounds decision variables from LP relaxation solution to construct a feasible integer solution
  - Only rounds decision variables with “large” fractional values
- Executes in $O(\mathbf{T}_{\text{LP}} + \boldsymbol{D}\tau\delta)$ time
- MAX Rounding is an α-approximation algorithm, where $\alpha = \max_{d \in D} \alpha_d$ and

$$\alpha_d \equiv (\Sigma_{v \in V} I_{vd})(\max_{j=1,2,\ldots,n_d} \Sigma_{t \in T} P_{djt})$$

Greedy Heuristic

- "Best Bang for the Buck" heuristic
  - Iteratively selects the "best" available vaccine that immunizes against the most disease doses
  - Does not require the solution of an LP

- Executes in $O(\boldsymbol{D}\tau\delta)$ time for each problem

- Greedy is an H_β -approximation algorithm for GMCVFSP-MED, where $\beta = \max_{v \in V}\{Val(v)\}$ and $H_k \equiv \Sigma_{i=1}^{k} \frac{1}{i}$

Computational Experiments

- Computational comparison of DP and IP (B&B)
- Two sets of test problems
  - 2006 Recommended Childhood Immunization Schedule (RCIS) using different scenarios (coded in MATLABv7.0)
  - Randomly generated “large” CIS with differing *valency* levels
    - DP coded in C
    - CPLEX 9.0 used to solve IP

Computational Experiments

2006 RCIS

Algorithm	Scenario 1			Scenario 2		
	Z	Time (sec)	θ	Z	Time (sec)	θ
MAX Rounding	499.05	0.13	1.00	736.77	0.13	1.02
Greedy	499.05	0.06	1.00	719.81	0.05	1.00
DP	499.05	0.32		719.81	0.30	
IP B&B	499.05	0.91		719.81	0.92	

- Scenario 1 uses currently licensed vaccines, where c_v = Federal contract purchase price for vaccine $v \in V$
- Scenario 2 uses currently licensed vaccines, where c_v = Federal contract purchase price for vaccine $v \in V$ + $10 (as a fixed cost of injection)
- $\theta = Z_{Heuristic}/Z^*$
- IP B&B is MATLAB's binary optimization solver

Computational Experiments

Large CIS

Val(*v*) ≤	DP CPU Time	IP (CPLEX) CPU Time	LP-IP GAP
3	9.27	0.88	1.01
4	11.65	20.82	1.02
5	14.51	958.56	1.03
6	17.01	501.74	1.05

- Size of each CIS: $\tau = 24$, $\delta = 17$, $\upsilon = 100$
- Averaged over 30 randomly generated CIS

Research Contributions

- Theoretical development of GMCVFSP
- Provides practical insights to policy makers, vaccine manufacturers, and pediatricians/public health administrators:
  - What is the economic impact of schedule changes?
  - What is the economic viability of combination vaccines?
  - How should new vaccines be priced?
  - What is the optimal vaccine formulary for a particular immunization environment?

Research Extensions

- Extend practicality and robustness of model
  - Different objective functions, additional immunization environment specific constraints, stochastic elements to DP
- Improve existing solution methodologies and/or develop new solution methodologies (both exact and heuristic)
- Extend model to other applications.