

Catch-up Scheduling for Childhood Vaccination

Faramroze G. Engineer, Pinar Keskinocak

Georgia Institute of Technology, fenginee@isye.gatech.edu, pinar@isye.gatech.edu

Larry K. Pickering

Centers for Disease Control and Prevention, lpickering@cdc.gov

In this paper, we outline the development of the core optimization technology used within a decision support tool to help providers and caretakers in constructing catch-up schedules for childhood immunization. These schedules ensure that a child continues to receive timely coverage against vaccine preventable diseases in the likely event that one or more doses have been delayed.

This work, a collaborative effort between the Centers for Disease Control and Prevention (CDC) and Georgia Institute of Technology, achieves a long-standing goal of providing a freely available and easy to use tool that removes from the task of constructing a catch-up schedule the tedious combinatorial aspects while maintaining a level of generality that allows easy accommodation for changes in the existing rules and adding new vaccines to the schedule lineup.

Although the catch-up scheduling problem is NP-hard, we develop a Dynamic Programming algorithm that exploits the typical size and structure of the problem to construct optimized schedules at almost the click of a button. In using an optimization based algorithm, our approach is unique not only in methodology but also in the information, strategy and advice we can offer to the user.

The tool is being advocated by both the CDC and the American Academy of Pediatrics (AAP) as a means of encouraging caretakers and providers to take a more proactive role in ensuring timely vaccination coverage of children under their care, as well as ensuring the accuracy and quality of a catch-up regime.

1. Introduction

With the goal of ensuring timely and accurate administration of vaccines, the Advisory Committee on Immunization Practices (ACIP) of the CDC together with the AAP and the American Academy of Family Physicians (AAFP) annually publish a *recommended* immunization schedule for children aged 0 to 6 years (see Figure 1 and CDC (2008c)). For a child who misses the recommended time for a dose, a healthcare professional faces the challenging task of constructing a *catch-up* schedule for that child under certain rules and guidelines for the administration of the remaining doses. These rules and guidelines specify the feasible number, timing and spacing of doses of each vaccine based on the child’s age, the number of doses already received, and the child’s age when each dose was previously administered (see Figure 2 and CDC (2008c) for a summary of guidelines for catch-up immunization).

Immunization programs have a significant impact on public health and have been shown

to be one of the most beneficial and cost effective disease prevention measures (Zhou et al. (2005) and Maciosek et al. (2006)). Although most school going children in the United States that are six years and over are deemed covered against vaccine preventable diseases, most do not receive the optimal protection due to incomplete, untimely or erroneous vaccination. A comprehensive study carried out by Luman et al. (2002) found that only 9% of children surveyed received all of their vaccinations at the recommended times and that only half received all their recommended doses by their second birthday. More recent data gathered as part of the National Immunization Survey (see CDC (2008b)) indicate only slight improvement in immunization coverage rates for individual vaccines. The introduction of new vaccines to the recommended schedule adds complexity and the potential for deterioration in the overall timeliness of vaccination. Once a child falls behind the recommended schedule, statistics indicate that they often do not catch-up until close to reaching a school going age when an accelerated

Figure 1 Recommended Immunization Schedule for Persons Aged 0-6 Years.

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Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2007

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B ¹	HepB		HepB	HepB	<i>see footnote 1</i>	HepB	HepB	HepB	HepB	HepB Series		
Rotavirus ²				Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis ³			DTaP	DTaP	DTaP		DTaP	DTaP				DTaP
<i>Haemophilus influenzae</i> type b ⁴			Hib	Hib	Hib ⁵	Hib	Hib	Hib	Hib			
Pneumococcal ⁵			PCV	PCV	PCV	PCV	PCV	PCV			PCV PPV	
Inactivated Poliovirus			IPV	IPV	IPV	IPV	IPV	IPV				IPV
Influenza ⁶							Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)	Influenza (Yearly)
Measles, Mumps, Rubella ⁷							MMR	MMR	MMR			MMR
Varicella ⁸							Varicella	Varicella	Varicella			Varicella
Hepatitis A ⁹							HepA (2 doses)	HepA (2 doses)	HepA (2 doses)		HepA Series	
Meningococcal ¹⁰											MPSV4	

Legend:

- Range of recommended ages
- Catch-up immunization
- Certain high-risk groups

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 0–6 years. Additional information is available at <http://www.cdc.gov/nip/recs/child-schedule.htm>. Any dose not administered at the recommended age should be administered at any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-822-7967.

regime is most likely administered to meet the minimum coverage mandated by most schools.

Several factors contribute to poor and untimely vaccination rates. Some, such as parental misunderstanding and logistical difficulties affected by various environmental and socioeconomic factors are generally difficult to address and remedy. However, the problem is often exacerbated by incomplete and inaccurate catch-up schedules constructed by healthcare professionals. Constructing an accurate catch-up schedule is both a challenging and time consuming task. It therefore comes as no surprise that healthcare professionals struggle to construct manually, catch-up schedules that reflect the best possible coverage for a child (Cohen et al. (2003) and Irigoyen et al. (2003)) and providers often fail to identify opportunities to vaccinate a child who may be at a clinic for purposes other than vaccination (Holt et al. (1996) and Szilagy et al. (1993)). The complexity of the task is highlighted by the survey carried out by Cohen et al. (2003) in which healthcare professionals were asked to construct catch-up schedules for 6 different hypothetical scenarios describing children who have fallen behind.

On average, only 1.83 out of the schedules constructed for the 6 scenarios were deemed correct. Indeed, 81% of the respondents were of the opinion that the catch-up regimes were “difficult or very difficult” to design.

In this paper, we investigate the catch-up scheduling problem and outline a Dynamic Programming (DP) algorithm that has been successfully adopted within a tool (downloadable from www.cdc.gov/vaccines/scheduler/catchup.htm) developed jointly by CDC and Georgia Institute of Technology to help caretakers and providers make timely and accurate decisions with regards to childhood vaccination.

1.1. Prevailing Technologies

The concept of a decision support tool to aid physicians in the important task of constructing catch-up schedules is not new. Currently, most Immunization Information Systems (formerly Immunization Registries) have some form of decision support tool for immunization scheduling (see CDC (2008a)). However, the availability and participation of providers in using Immunization Information Systems vary wildly by state and the type of provider (Rasulnia and Kelly (2006)). Furthermore, these tools are

Figure 2 Guidelines for Catch-up Immunization Scheduling

CATCH-UP SCHEDULE FOR PERSONS AGED 4 MONTHS–6 YEARS					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B ¹	Birth	4 weeks	8 weeks (and 16 weeks after first dose)		
Rotavirus ²	6 wks	4 weeks	4 weeks		
Diphtheria, Tetanus, Pertussis ³	6 wks	4 weeks	4 weeks	6 months	6 months ³
Haemophilus influenzae type b ⁴	6 wks	4 weeks if first dose administered at age <12 months	4 weeks ⁵ if current age <12 months	8 weeks (as final dose) if current age ≥12 months and second dose administered at age <15 months	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months
		8 weeks (as final dose) if first dose administered at age 12–14 months	8 weeks (as final dose) ⁴ if current age ≥12 months and second dose administered at age <15 months	No further doses needed if first dose administered at age ≥15 months	No further doses needed if previous dose administered at age ≥15 months
		No further doses needed if first dose administered at age ≥15 months	No further doses needed if previous dose administered at age ≥15 months		
Pneumococcal ⁵	6 wks	4 weeks if first dose administered at age <12 months and current age <24 months	4 weeks if current age <12 months	8 weeks (as final dose) if current age ≥12 months	8 weeks (as final dose) This dose only necessary for children aged 12 months–5 years who received 3 doses before age 12 months
		8 weeks (as final dose) if first dose administered at age ≥12 months or current age 24–59 months	8 weeks (as final dose) if current age ≥12 months	No further doses needed for healthy children if first dose administered at age ≥24 months	No further doses needed for healthy children if previous dose administered at age ≥24 months
		No further doses needed for healthy children if first dose administered at age ≥24 months	No further doses needed for healthy children if previous dose administered at age ≥24 months		
Inactivated Poliovirus ⁶	6 wks	4 weeks	4 weeks	4 weeks ⁶	
Measles, Mumps, Rubella ⁷	12 mos	4 weeks			
Varicella ⁸	12 mos	3 months			
Hepatitis A ⁹	12 mos	6 months			

somewhat limited with regards to the length of the scheduling horizon (i.e., only give a schedule for the current and next doses that are due), and follow rule-based decision making (also known as expert systems) that sequentially go through and schedule each vaccine individually (Miller et al. (1997) and Miller (1997)). There are several drawbacks to this approach. First, when there are changes in the rules or addition of new vaccines, the internal logic behind the tool needs to be updated as well, which is often a lengthy process in the order of months. Second, sequential decision making cannot effectively optimize a schedule under rules that couple together the decision making for scheduling doses of different vaccines. With the growing number of vaccines and introduction of new combination vaccines, functionality that captures the coupling effects of different vaccines within a decision support tool has become increasingly important and clearly, the availability and scope of the current technologies are soon to be inadequate in coping with the needs of a provider or caretaker.

In what follows, we give a precise description of the catch-up scheduling problem in §2, a brief outline of relevant literature in §3, analyze the complexity of the problem in §4, discuss

our experience with optimization techniques (in particular dynamic programming) as a possible solution approach in §5, present solutions obtained for two real-life scenarios in §6, and relay some preliminary statistics about the use of the tool and initial feedback from both physicians and parent in §7.

2. Problem Description and Notation

Given the current age of a child and their vaccination history (i.e., the number and timing of doses of each vaccine already administered), the catch-up scheduling problem is one of constructing a schedule for the remaining doses so that each dose is scheduled within the minimum and maximum age for that vaccine and dose, and the time separation between (not necessarily successive) doses of the same vaccine does not violate a certain minimum gap. This minimum gap may vary by vaccine, dose, current age and/or age at which some previous dose is administered. For example, the minimum gap between the second and third dose of *Hib* is 4 weeks if the current age is < 12 months, and the minimum gap is 8 weeks if the current age is ≥ 12 months and the second dose is administered at age < 15 months. In addition to regulating the gap between doses of the same vaccine,

¹ A “live virus” vaccine is a vaccine that contains a “living” virus that is able to give and produce immunity, usually without causing illness.

doses of *live*¹ vaccines can only be administered during the same visit or at least a certain number of fixed days apart (28 days under the current guidelines). Finally, the number of *simultaneous administrations* (i.e., number of vaccinations administered during a single visit) may be discretionarily limited to avoid significant discomfort to a child.

Note that even without imposing a limit on the number of simultaneous vaccinations, it may not be possible to construct a schedule in which all the remaining doses can be feasibly scheduled. If a dose for some vaccine cannot be scheduled, the vaccination *series* for that vaccine is considered incomplete.

In certain cases depending on the child's age and/or the age at which some previous dose is given, it may be beneficial or necessary to prematurely terminate a series. For example, a child normally receives 4 doses of *PCV*, however, the second dose is deemed final if the first dose is administered at age ≥ 12 months or the current age is 24-59 months. In either case, the third and fourth doses are unnecessary. This form of *contraindication* can be captured by setting the required gap between the appropriate pair of doses to infinity for the appropriate range for the current age and the age when the earlier dose in the pair is administered. For example, Table 1 demonstrates how one can capture the required spacing and contraindication between the first dose and each subsequent dose of *PCV*. Note that in addition to the contraindication mentioned earlier, if the first dose of *PCV* is given on or after 24 months, then all subsequent doses are contraindicated.

Given the structure of the rules governing the spacing between doses, it maybe possible to force a contraindication by unnecessarily delaying the administration of some dose. Thus, when constructing a schedule, we are required to maximize the number of completable vaccination series, and among such candidate schedules, maximize the total number of scheduled doses and minimize the total delay from the recommended age of administering these doses.

We next introduce notation characterizing the catch-up scheduling problem more formally:

V	the set of vaccines.
n_v	the total number of doses that constitute the completion of a vaccination series of $v \in V$.
$t_{v,i}^{min}$	the minimum age for administering dose $i \in \{1, \dots, n_v\}$ of $v \in V$.
$t_{v,i}^{max}$	the maximum age for administering dose $i \in \{1, \dots, n_v\}$ of $v \in V$.
$t_{v,i}^{rec}$	the recommended age for administering dose $i \in \{1, \dots, n_v\}$ of $v \in V$.
$t_{v,i,j}^{gap}(t_i, t_j)$	the minimum gap required between dose i and dose $j > i$ of vaccine v when i is administered at age t_i , and j is being considered for administration at age t_j .
$V^{live} \subseteq V$	the set of live vaccines.
t^{live}	the minimum gap required between doses of any live vaccines when they are not administered during the same visit.
M	the maximum number of simultaneous administrations.

Given a schedule denoted by s , we use the following notation to define the number and timing of doses scheduled along with some other characteristics of s :

$n_v(s)$	the number of doses of vaccine v that have been scheduled in s .
$t_{v,i}(s)$	is the age at which dose $i \in \{1, \dots, n_v(s)\}$ of v is scheduled in s .
$m(s, t)$	the number of vaccinations scheduled at age t , i.e., $m(s, t) = \{v \in V : t_{v,i}(s) = t \text{ for some } i\} $.
$c(s)$	the number of completable vaccination series, i.e., $c(s) = \{v \in V : n_v = n_v(s)\} $.
$n(s)$	the total number of doses scheduled, i.e., $n(s) = \sum_{v \in V} n_v(s)$.
$d_{v,i}(s)$	the delay from the recommended age of administering dose i of vaccine v , i.e., $d_{v,i}(s) = \max\{0, t_{v,i}(s) - t_{v,i}^{rec}\}$.
$d(s)$	the total delay from the recommended age of administering the scheduled doses, i.e., $d(s) = \sum_{v \in V} \sum_{i=1}^{n_v(s)} d_{v,i}(s)$.
$t(s)$	an age after which no doses have been scheduled, i.e., $t(s) \geq t_{v,i}(s)$ for all $i \in \{1, \dots, n_v(s)\}$ and $v \in V$.

For a given schedule s , we can then define feasibility as follows: A schedule s is feasible if

Table 1 The spacing between the first dose and remaining doses of PCV

dose i	dose $j > i$	age i is administered	age j is considered for administration	min gap between i and j
1	2	[0,12 months)	$[0, \infty)$	4 weeks
1	3	[0,12 months)	$[0, \infty)$	8 weeks
1	4	[0,12 months)	$[0, \infty)$	16 weeks
1	2	[12 months, $\infty)$	$[24, 60 \text{ months})$	8 weeks
1	3,4	[12 months, $\infty)$	$[24, 60 \text{ months})$	∞
1	2, 3, 4	[24 months, $\infty)$	$[0, \infty)$	∞

F-1. s satisfies the time windows for individual doses, i.e. $t_{v,i}^{min} \leq t_{v,i}(s) \leq t_{v,i}^{max}$ for all $i \in \{1, \dots, n_v(s)\}$ and $v \in V$.

F-2. s satisfies the gap requirements between doses of the same vaccine, i.e., $t_{v,j}(s) - t_{v,i}(s) \geq t_{v,i,j}^{gap}(t_{v,i}(s), t_{v,j}(s))$ for all $i \in \{1, \dots, n_v(s)\}$, $j \in \{i+1, \dots, n_v(s)\}$ and $v \in V$.

F-3. s satisfies the gap requirement between doses of live vaccines, i.e.,

$$|t_{w,j}(s) - t_{v,i}(s)| \begin{cases} = 0, & \text{or} \\ \geq t^{live} \end{cases}$$

for all $i \in \{1, \dots, n_v(s)\}$, $j \in \{1, \dots, n_w(s)\}$ and $v, w \in V^{live}$.

F-4. No more than M doses are scheduled in s at any given age, i.e. $m(s, t) \leq M$ for all t .

We say that a schedule s' is an *extension* of schedule s , if s' can be obtained from s by scheduling any remaining doses of s after $t(s)$.

The catch-up scheduling problem can then be stated as follows: Given a feasible schedule s , the catch-up scheduling problem is one of extending s to a feasible schedule s^* so that

$$\begin{bmatrix} c(s^*) \\ n(s^*) \\ -d(s^*) \end{bmatrix} \geq_L \begin{bmatrix} c(s') \\ n(s') \\ -d(s') \end{bmatrix}$$

for any other feasible extension s' of s . Here we use \geq_L to represent a lexicographical ordering of vectors. Thus, s^* is the best extension of s with respect to (1) the number of completable vaccination series, (2) the number of scheduled doses, and (3) the total delay from the recommended age of administering the scheduled doses, in the stated order of priority.

3. Similarities with Traditional Scheduling Problems

There exists an extensive amount of research and literature focused on scheduling and

sequencing problems. The reader is referred to Brucker (2004), Pinedo (2002) and Chretienne et al. (1995) for a thorough exposition on a variety of scheduling problems, complexity results and solution approaches. Of particular interest to us are scheduling problems with simple “chain” type precedence constraints that are analogous to scheduling doses of a vaccination series.

The catch-up scheduling problem can be viewed as a multi-processor scheduling problem where a job corresponds to a particular dose of some vaccine, and we have chain type precedence requirements for jobs corresponding to doses belonging to the same vaccine to ensure that the doses are scheduled in sequence. The number of available processors corresponds to the maximum number of simultaneous administrations. In addition to chain type precedence constraints, each job has a unit processing time, release and due dates corresponding to the allowable window for administering a dose, variable separation times between jobs corresponding to the doses of the same vaccine, and fixed separation times between jobs corresponding to the doses of live vaccines. Following are just a few relevant examples from a much broader spectrum of work on scheduling that share characteristics with the catch-up scheduling problem.

Brucker et al. (1999), show that the two-machine scheduling problem with chain precedence and unit execution times is solvable in linear time when minimizing makespan. Jansen et al. (1995) show that the identical problem when forcing jobs to be executed on one of the two machines is NP-complete. They give an approximation scheme for minimizing the makespan of the schedule. Chu and Proth (1994), analyze a similar one-machine problem except the hardness in their problem arises

from non-unit execution times and the requirement of spacing consecutive jobs in a chain within a given minimum and maximum value. They use a branch-and-bound algorithm to find the optimal schedule, and use a heuristic policy to find schedules for intractable instances. Wikum et al. (1994) analyze an identical problem with the addition of release dates. They note that the problem is easy to solve if each chain consists of a single job, and give a polynomial algorithm to solve the problem under these assumptions. Drora et al. (1997), show that chain scheduling problem without release dates and separation requirements remains NP-complete when the objective is to minimize the total completion times rather than makespan. They also point out that a variation of the problem where jobs belonging to the same chain have to be processed on the same machine can be polynomially solved. Finally, Kubiak et al. (1998) prove that two-machine scheduling problem with chain precedence, unit execution times and no more than two jobs per chain is polynomial solvable in the presence of a single resource constraint.

While the catch-up scheduling problem encapsulates many of the complexities of the above mentioned scheduling problems, it differs from them in that it may not be possible to construct a feasible schedule with all remaining doses and since the required separation between doses varies with not only the current age of the child but also, the age at which some previous dose is administered. As a result, one has to employ a multi-level objective that is not typically found in literature but at the same time, ideally suited for DP.

4. Problem Complexity

We next highlight some of the main complexities of the catch-up scheduling problem by showing that the problem remains NP-complete under various simplifications. The analysis helps us identify some of the complicating characteristics that need to be addressed in the design of the DP algorithm outlined in the next section.

PROPOSITION 1. *The catch-up scheduling problem is NP-complete without any restrictions on the minimum gap between doses and without live vaccines.*

Proof We prove by reduction from the well known NP-complete *Set Packing* problem (see Garey and Johnson (1979)) defined as follows: *INPUT:* A set of subsets $\mathcal{Q} = \{Q_1, \dots, Q_m\}$ of the universal set $\mathcal{U} = \{1, \dots, n\}$.

QUESTION: What is the largest packing (i.e. number of disjoint subsets) of \mathcal{Q} ?

For convenience, we may assume without loss of generality that for each $i = 1, \dots, m$, the set $Q_i = \{q_{i,1}, q_{i,2}, \dots\}$ is ordered such that $q_{i,j} < q_{i,j+1}$ for all $j = 1, \dots, |Q_i| - 1$. Thus, $\{1, \dots, m\}$ can be viewed as the set of vaccines and $q_{i,j}$ the age at which dose j of vaccine i must be administered. The corresponding instance of the catch-up scheduling problem can then be obtained as follows:

- $V = \{v_1, \dots, v_m\}$,
- $n_{v_i} = |Q_i|$ for $i = 1, \dots, m$,
- $t_{v_i,j}^{\min} = t_{v_i,j}^{\max} = t_{v_i,j}^{\text{rec}} = q_{i,j}$ for all $i = 1, \dots, m$ and $j = 1, \dots, n_{v_i}$,
- $t_{v_i,j,k}^{\text{gap}}(t_j, t_j) = 0$ for all $i = 1, \dots, m$, $j = 1, \dots, n_{v_i}$, $k = j + 1, \dots, n_{v_i}$, t_j , and t_k ,
- $V^{\text{live}} = \emptyset$,
- $t^{\text{live}} = 0$, and
- $M = 1$.

Let s be an empty schedule (i.e., without any doses scheduled) and $t(s) = 0$.

Observe that a series of vaccine v_i can be completed only if each dose $j \in \{1, \dots, |Q_i|\}$ is scheduled at exactly the age $q_{i,j}$. Thus, since $M = 1$ (i.e., no two vaccinations can be given at the same age), finding a maximum packing is equivalent to finding an extension of s with the most number of completable vaccination series. \square

PROPOSITION 2. *The catch-up scheduling problem is NP-complete without any restrictions on the maximum age for a dose and without live vaccines.*

Proof We again prove by reduction from the NP-complete *Set Packing* problem defined earlier in the proof of Proposition 1:

- $V = \{v_1, \dots, v_m\}$,
- $n_{v_i} = |Q_i| + 1$ for $i = 1, \dots, m$,

- $t_{v_i,j}^{min} = t_{v_i,j}^{rec} = q_{i,j}$ for all $i = 1, \dots, m$ and $j = 1, \dots, n_{v_i} - 1$,
- $t_{v_i,n_{v_i}}^{min} = t_{v_i,n_{v_i}}^{rec} = n + i$ for all $i = 1, \dots, m$,
- $t_{v_i,j}^{max} = \infty$ for all $i = 1, \dots, m$ and $j = 1, \dots, n_{v_i}$,
- $t_{v_i,j,k}^{gap}(t_j, t_k) = \begin{cases} 0, & t_j = t_{v_i,j}^{min} \\ \infty, & \text{otherwise} \end{cases}$ for all $i = 1, \dots, m, j = 1, \dots, n_{v_i}, k = j + 1, \dots, n_{v_i}$, and t_k ,
- $V^{live} = \emptyset$,
- $t^{live} = 0$, and
- $M = 1$.

Let s be an empty schedule (i.e. without any doses scheduled) and $t(s) = 0$.

Observe that a series of vaccine v_i can be completed only if each dose $j \in \{1, \dots, |Q_i|\}$ is scheduled at exactly the age $q_{i,j}$. Indeed, if a dose j is scheduled after $q_{i,j}$, then any remaining doses after j (of which there is at least one) cannot be scheduled since the minimum gap would be ∞ . Note that if the first $n_{v_i} - 1$ doses can be scheduled at age $q_{i,j}$ for each $j \in \{1, \dots, |Q_i|\}$, then the last dose can always be scheduled at an age that does not interfere with any dose of any other vaccine. Thus, since $M = 1$ (i.e. no two vaccinations can be given at the same age), finding a maximum packing is equivalent to finding an extension of s with the most number of completable vaccination series. \square

PROPOSITION 3. *The catch-up scheduling problem is NP-complete without any restriction on the number of simultaneous administrations.*

Proof We yet again prove by reduction from the NP-complete *Set Packing* problem defined earlier. This time however, we use the restrictions imposed by live vaccines:

- $V = \{v_1, \dots, v_m\}$,
- $n_{v_i} = |Q_i|$ for $i = 1, \dots, m$,
- $t_{v_i,j}^{min} = t_{v_i,j}^{max} = t_{v_i,j}^{rec} = 2 \max\{m, n\}(q_{i,j} - 1) + i$ for all $i = 1, \dots, m$ and $j = 1, \dots, n_{v_i}$,
- $t_{v_i,j,k}^{gap}(t_j, t_k) = 0$ for all $i = 1, \dots, m, j = 1, \dots, n_{v_i}, k = j + 1, \dots, n_{v_i}, t_j$ and t_k ,
- $V^{live} = V$,
- $t^{live} = \max\{m, n\}$, and
- $M = \infty$.

Let s be an empty schedule (i.e. without any doses scheduled) and $t(s) = 0$.

Firstly, observe that a series of vaccine v_i can be completed only if each dose $j \in$

$\{1, \dots, |Q_i|\}$ is scheduled at exactly the age $2 \max\{m, n\}(q_{i,j} - 1) + i$. Next observe that if $q_{i,j} = q_{k,l}$, then doses j and l of vaccines i and k respectively cannot both be part of a feasible schedule. Indeed, $|(2 \max\{m, n\}(q_{i,j} - 1) + i) - (2 \max\{m, n\}(q_{k,l} - 1) + k)| = |k - i|$, when $q_{i,j} = q_{k,l}$. Thus, doses j and l cannot be administered at the same age or at least $t^{live} = \max\{m, n\}$ apart since $0 < |k - i| < m \leq \max\{m, n\}$ when $k \neq i$. Conversely, if the gap between the only allowable time to administer dose j of vaccine i and dose l of vaccine k is greater than 0 but less than $t^{live} = \max\{m, n\}$, then it must be the case that $q_{i,j} = q_{k,l}$. Thus, finding a maximum packing is equivalent to finding an extension of s with the most number of completable vaccination series. \square

5. Solution Approach

Although, the catch-up scheduling problem is theoretically intractable, the typical size of the catch-up scheduling problem does not pose a huge challenge in terms of ultimately being able to solve these problems. Instead, the challenge we face is in being able to solve these problems consistently within a short amount of time (generally a few seconds).

5.1. An Integer Programming model

Integrating an Integer Programming (IP) solver such as the free to use Branch-and-Cut solver provided by COIN-OR (www.coin-or.org) within an automated tool although not a trivial task, is a reasonably quick and fairly straightforward process and thus, was the obvious choice as a starting point to solve the catch-up scheduling problem.

By assigning binary variables to decisions corresponding to administering a dose of some vaccine at a given point in time chosen within a predefined time discretization, we were able to model the catch-up scheduling problem with a natural time expanded formulation. In all, instances of the catchup scheduling problem typically required approximately 1,700 to 2,500 binary variables and about 600 constraints half of which correspond to the constraints that couple together the timing and spacing of live-virus vaccines.

We encountered several difficulties with the development and solution process of the IP model. Primary of these was having to quantify all objective measures within a single objective function. Recall that the paradigm for constructing catch-up schedules has a clearly defined hierarchy that requires us to maximize the number of completable vaccination series first before trying to maximize the number of doses and minimize the total delay in administering doses. We tried to emulate this structure using a hierarchy of penalties in the objective that favored the completion of a vaccination series over the number of doses scheduled and the delay in administering doses. Unfortunately, the interaction of the large penalties for skipping a dose with the penalties for delaying administrations made the IP unstable in certain cases requiring far too much computation time for an online tool. The problem was exacerbated by the fact that the feasible solutions found early on in the process, were either of poor quality or nonsensical even if they had relatively small provable gaps.

On examining the problematic instances and the fractional solutions they tended to favor, we noticed a common theme: In most of these instances, there were doses that were well overdue and by choosing not to administer the dose immediately, the dose may then fall within the window of contraindication. Although we use penalties to ensure this does not occur in any optimal integer solution, it may indeed be the case that the fractional solutions prefer to push-back administering a dose in the hope that it is contraindicated and thus we do not pay the penalty for administering a delayed dose. This form of gaming is clearly contrary to the paradigm for constructing catch-up schedules.

To counter some of these difficulties, we used priority branching that favors decision variables corresponding to doses that are well overdue and/or on the verge of being contraindicated and included additional constraints that enforced a certain minimum number of doses are always scheduled for each vaccine. In addition, we toiled with several alternative formulations with fewer variables in the objective with large penalties at the expense of more auxiliary

decision variables. We also relaxed some of the problematic constraints that couple together the decision making of different vaccines such as limiting the number of simultaneous administrations and regulating the gap between live vaccines. Depending on the tightness of the limit on number of simultaneous administrations, we only enforced this constraint for the first few weeks of the future schedule horizon and ignored the constraints coordinating the schedule of live vaccines altogether. On the off-chance that the optimal solution violates some of these conditions, we were often able to correct the schedules heuristically by pushing-back some doses without changing the schedule too much. Rarely did we come across instances for which we could not fix the solutions.

These simple schemes together with tuning the cut and pre-processing parameters of the solver brought down the solution times from several minutes on average and up-to half an hour for some instances, to few tens of seconds on average and no more than a minute. Although a vast improvement, we still needed a certain worst-case guarantee of the runtime that scales better than the IP. This prompted us to investigate the possibility of using DP.

5.2. A DP Algorithm

In this section, we outline a DP algorithm for solving the catch-up scheduling problem. We start by identifying “dominance” of one schedule over another.

DEFINITION 1 (DOMINANCE). Given two feasible schedules s_1 and s_2 such that $t = t(s_1) = t(s_2)$, we say s_1 dominates s_2 or $s_1 \preceq s_2$, if we can extend s_1 to a schedule that is at least as good as any schedule obtained from extending s_2 .

Clearly, only non-dominated schedules are warranted in the construction of the optimal schedule. Unfortunately, given the complexity of the problem, it is unlikely that there exist efficient necessary conditions for proving dominance of one schedule over another. However, we can find reasonable sufficient conditions by observing that the required spacing between a pair of doses of the same vaccine is generally non-decreasing in the age the first dose in the pair is administered. Using this observation, we can

identify within a given schedule certain vaccine-dose pairs that are deemed “critical” for the timing, spacing and/or contraindication of any remaining doses. We define the following to identify these critical vaccine-dose pairs for a feasible schedule s :

$$\Psi(s) = \left\{ (v, i) : \begin{array}{l} v \in V, i \in \{1, \dots, n_v(s)\} \\ \text{such that either:} \\ \text{i. } t_{v,i}(s) + t_{v,i,j}^{gap}(t_{v,i}, t') > t' \\ \text{for some} \\ j \in \{n_v(s) + 1, \dots, n_v\} \\ \text{and } t' \geq t(s), \text{ or} \\ \text{ii. } t_{v,i}(s) + t^{live} > t(s) \text{ and} \\ v \in V^{live} \end{array} \right\}.$$

Dominance can then be recognized by using the criteria set out in the following proposition when assuming that the spacing required between doses is non-decreasing in the age the first dose in the pair is scheduled.

PROPOSITION 4. *If $t_{v,i,j}^{gap}(t_i, t_j)$ is non-decreasing in t_i for all $v \in V, i \in \{1, \dots, n_v\}, j \in \{i + 1, \dots, n_v\}$, and t_j , then for any two feasible schedules s_1 and s_2 such that $t = t(s_1) = t(s_2)$, $s_1 \preceq s_2$ whenever:*

D-1. $n_v(s_1) \geq n_v(s_2)$ for all $v \in V$,

D-2. $n_v(s_1) = n_v(s_2)$ for all $v \in V^{live}$ s.t. $(v, n_v(s)) \in \Psi(s)$,

D-3. $t_{v,i}(s_1) \leq t_{v,i}(s_2)$ for all $(v, i) \in \Psi(s_1)$ such that $i \in \{1, \dots, n_v(s_2)\}$, and

D-4. $\sum_{v \in V} \sum_{i=1}^{n_v(s_2)} d_{v,i}(s_1) \leq \sum_{v \in V} \sum_{i=1}^{n_v(s_2)} d_{v,i}(s_2)$.

The dominance criteria simply state that s_1 dominates s_2 if (1) s_1 has scheduled at least as many doses as s_2 for each vaccine, (2) s_1 has scheduled the same number of doses as s_2 for any live vaccine whose last dose in s_1 prohibits the scheduling of any other live vaccine at age t , (3) the timing of critical doses scheduled in s_1 is no later in s_1 than in s_2 , and (4) the total delay in administering doses in common is no worse in s_1 than in s_2 .

If the required gap between a pair of doses is non-decreasing in the age the first dose is scheduled, then intuitively it makes sense that a schedule with the critical doses scheduled earlier has more flexibility for scheduling future doses. The remaining non-critical doses play no part in

determining the flexibility available for scheduling the remaining doses but may contribute to the overall quality of the schedule. The proof of the validity of this dominance criteria is given in the appendix.

Algorithm 1 The DP Algorithm

Input: schedule s .

Initialize:

planning horizon $\tau(s) = \{t_1, \dots, t_{|\tau(s)|}\}$,

$\mathcal{S}(t_0) \leftarrow \{s\}$, and

$\mathcal{S}(t_k) \leftarrow \{\emptyset\}$ for all $k = 1, \dots, |\tau(s)|$.

Main Loop:

for $k = 1, \dots, |\tau(s)|$ **do**

 /* Iteration k */

for all $s' \in \mathcal{S}(t_{k-1})$ **do**

for all $V' \subseteq V$ s.t. $|V'| \leq M$ **do**

if $\langle s', V', t_k \rangle$ is feasible **then**

if $s'' \not\preceq \langle s', V', t_k \rangle$ for any $s'' \in \mathcal{S}_{t_k}$

then

 remove from \mathcal{S}_{t_k} any schedule s''

 s.t. $\langle s', V', t_k \rangle \preceq s''$, and

$\mathcal{S}_{t_k} \leftarrow \mathcal{S}_{t_k} \cup \{\langle s', V', t_k \rangle\}$

end if

end if

end for

end for

end for

Output: schedule $s^* \in \mathcal{S}_{t_{|\tau(s)|}}$ such that

$\overline{[c(s^*), n(s^*), -d(s^*)]} \geq_L [c(s'), n(s'), -d(s')]$

for all $s' \in \mathcal{S}_{t_{|\tau(s)|}}$.

Given criteria for efficiently recognizing dominance, we can then use the DP algorithm outlined in Algorithm 1 to construct the optimal schedule. We start by discretizing the planning horizon available to us to schedule the remaining doses. The discretization is chosen so that we do not delay administering an overdue dose too much while leaving sufficient time between discretization points to avoid frequent visits to a clinic. Typically in practice, a weekly discretization is used. For a given schedule s , we define $\tau(s) = \{t_1, t_2, \dots, t_{|\tau(s)|}\}$ to be the ordered set of time points corresponding to possible ages a dose can be administered starting with $t_1 > t(s)$. Thus, starting with s and age $t_0 = t(s)$, the DP algorithm at each iteration

constructs for some time point t_k , all possible schedules that can be obtained by extending all non-dominated schedules constructed for age t_{k-1} . Here, we denote with $\langle s', V', t \rangle$, the new schedule resulting from extending schedule s' by scheduling each vaccine in the set $V' \subseteq V$ at age t and setting $t(\langle s', V', t \rangle) = t$. Any newly constructed schedule that is either infeasible or dominated by an existing schedule is immediately discarded. Otherwise, the algorithm discards any schedule that may instead be dominated by the newly constructed schedule.

PROPOSITION 5. *At the end of iteration k of Algorithm 1, \mathcal{S}_{t_k} contains all non-dominated extensions of schedule s that do not have any doses scheduled after age t_k .*

Proof Let s' be a feasible extension of s such that $t(s') = t_k$. We prove by induction on k that at the end of iteration k , there exists $s^* \in \mathcal{S}_{t_k}$ such that $s^* \preceq s'$.

If $k = 1$, let V' be the set of vaccines that are scheduled at age t_1 in s' . Since $s' = \langle s, V', t_1 \rangle$, and $\mathcal{S}_{t_0} = \{s\}$, s' must have been constructed during iteration 1. Thus, if $s' \notin \mathcal{S}_{t_1}$, at the end of iteration 1, then it must have been discarded due to dominance, i.e. there exists $s^* \in \mathcal{S}_{t_1}$ such that $s^* \preceq s'$.

Suppose $k > 1$ and let V' be the set of vaccines that are scheduled at age t_k in s' . Let s'' be the schedule obtained by removing vaccines V' from s' , i.e. $s'' = \langle s'', V', t_k \rangle$. By induction, there exists $s^{*''} \in \mathcal{S}_{t_{k-1}}$ such that $t(s^{*''}) = t(s'')$ and $s^{*''} \preceq s''$. Let $s^{*''}$ be the best extension of $s^{*''}$, and let V'' be the vaccines scheduled on day t_k in $s^{*''}$. Since $s^{*''} \preceq s''$, it follows from definition of dominance that any extension of s'' can be no better than the best extension of $s^{*''}$. Thus, we must have $s^{*'} = \langle s^{*''}, V'', t_k \rangle \preceq s' = \langle s'', V', t_k \rangle$. Finally, since $s^{*''} \in \mathcal{S}_{t_{k-1}}$, it follows that $s^{*'}$ must have been constructed during iteration k . Thus, if $s^{*'}$ is not in \mathcal{S}_{t_k} by the end of iteration k , then it must have been discarded due to dominance, i.e. there exists $s^* \in \mathcal{S}_{t_k}$ such that $s^* \preceq s'$. \square

COROLLARY 1. *At the end of iteration k of Algorithm 1, \mathcal{S}_{t_k} contains the best extension of s that does not have any doses scheduled after age t_k .*

Thus, starting with a partial schedule containing only the past vaccination history of the child, the DP constructs the optimal schedule for administration of the remaining doses. Using the given dominance criteria, we are able to solve most instances within a second and have never encountered any practical instance that took longer than a handful seconds to solve.

Note that if there is no limit on the number of simultaneous administrations, and no live vaccines, then there would be no reason to delay administration of some overdue dose. Indeed, in this case, for a given schedule s' and feasible extensions $\langle s', V', t \rangle$ and $\langle s', V'', t \rangle$, it follows from Proposition 4 that $\langle s', V', t \rangle \preceq \langle s', V'', t \rangle$ if $V'' \subseteq V'$. Thus, one can construct an optimal extension of a given schedule by simply scheduling sequentially in time all vaccines that can be feasibly scheduled at a given age. This leads to an algorithm that is linear in the number of time points.

Even if there are live vaccines, the current rules require a spacing of 28 days when they are not scheduled during the same visit. Thus, since the required spacing between doses of the same vaccine is at least four weeks in most cases and since we use a weekly discretization, enforcing the spacing between live vaccines does not in practice have a huge impact on the size of the state-space explored by the DP algorithm.

5.3. Practical Issues

The following are some of the more practical considerations made to ensure the day-to-day practicality, usefulness, and long-term sustainability of the solution approach within a decision support tool.

5.3.1. Regular Versus Accelerated Schedules. Once a child has caught-up to the original schedule for some vaccine, it is then undesirable to administer any subsequent doses before the recommended age if possible. In this case, we penalize both the delay and premature scheduling of any subsequent doses. On the other hand, rather than target the recommended age, in an *accelerated* schedule the doses are scheduled as soon as feasibly possible. Accelerated schedules may be preferable in cases where a child comes from a historically high risk demographic, or if they have a

sporadic vaccination history. Constructing an accelerated schedule is easily achieved by simply setting the recommended age to the earliest possible time for administering a dose. In the tool, the user is given the choice to construct a regular schedule as well as an accelerated schedule.

5.3.2. Combination Vaccines. The use of *combination* vaccines, which combine two or more vaccinations within a single shot, is another practical consideration of note. Simultaneous administration of vaccines under the guidelines set out by ACIP is an encouraged practice (see recommendations in Plotkin and Orenstein (2004) and Atkinson et al. (2006)) since studies have shown that this practice places almost no additional burden on the immune system of a healthy child. Combination vaccines thus, allow for equal coverage with less discomfort to a child.

One can administer a combination vaccine only if it is feasible to administer each individual vaccine in the combination. Although we have not explicitly included this as part of our model, we can ensure vaccines bundled within a combination are scheduled together by simply enforcing that the subset of vaccines V' that is used to extend a schedule in the DP algorithm contains either all the vaccines in a given combination or none of them. In this way, vaccines belonging to the same combination are always aligned to be scheduled at the same age.

5.3.3. Dealing with an Infeasible Vaccination History. The DP algorithm works under the premise that the schedule we start with is feasible. This may not necessarily be the case if a child's vaccination history is used as the starting point. It may be the case that the user has simply entered data incorrectly or, the child has actually received an incorrect dose in the past. In either case, we use the feasibility checker within the DP to check the feasibility of the starting schedule and warn the user if there are any irregularities. If it is confirmed that a dose has been incorrectly administered in the past, the user is prompted to remove such doses from the vaccination history to allow the scheduler to reschedule the dose.

5.3.4. Testing and Piloting. To ensure the tool is accurate, easy to use and reflects the current and future needs of providers and caretakers, we have collaborated closely with both the rule makers and the potential users. A beta version of the tool was demonstrated at the AAP National Conference and Exhibition (NCE) 2007 and presented to the Committee on Infectious Diseases (COID) as well as several pediatric clinics in Atlanta, GA. The feedback gathered was used to develop the user interface and design the output to best meet the needs of caretakers and providers.

5.3.5. A Vaccine Modeling Language. When new vaccines are added to the lineup, or modifications are made to the rules for existing vaccines, the core optimization technology remains unchanged. Although this seems like an obvious statement, it is of vital importance for the sustainability of the tool within an environment where the people responsible for updating the tool may not be familiar with optimization or optimization based technologies. The tool contains an external wrapper called the Vaccine Modeling Language (VML) that allows authorized persons to add new vaccines or modify the characteristics of existing vaccines easily without having to change the fundamental components of the algorithm. The VML is a tabular encapsulation of all the characteristics that define the rules and guidelines for each vaccine. Here, an expert user may set such input as the number of doses for a new vaccine, the minimum and maximum age for each dose, and a matrix as shown in Table 1 to regulate the gap between two doses given the current age of the child and the age at which the first dose in the pair is administered.

6. A Case Study of Two Scenarios

In this section, we present four solutions obtained for two different real-life scenarios for children requiring catch-up schedules. These cases present varying levels of urgency in terms of how far behind a child has fallen as well as demonstrate the action/in-action of different rules that govern the timing, spacing and premature termination of a series.

Figure 3 A catch-up schedule constructed for Case 1.

Schedule generated for: ***** on Apr 21, 2008 (04/21/2008)
Birth Date: Dec 21, 2007 (12/21/2007). Current Age: 0 year/s, 4 month/s and 0 week/s

Age	0-4 weeks	1-3 months	3-6 months			6-12 months	12-15 months	15-18 months		18-24 months	3-4 years	4-6 years	Tally
Rec. Date (mm/dd/yy)	12/21/07	02/21/08	Today 04/21/08	05/19/08	06/16/08	12/15/08	03/09/09	04/10/09	06/19/09	11/20/09	12/12/11	12/13/13	
HepB	AD	AD			OD								3/3
Rota													0/3
DTaP		AD	CD		OD		OD				OD		5/5
Hib		AD	CD		OD	OD							4/4
PCV		AD	CD		OD	OD							4/4
IPV			CD	CD	OD						OD		4/4
MMR						OD					OD		2/2
Var						OD					OD		2/2
HepA						OD			OD				2/2

AD - Administered Dose CD - Catch-up Dose OD - On-time Dose PD - Preemptive Dose

Figure 4 An accelerated schedule constructed for Case 1.

Schedule generated for: ***** on Apr 21, 2008 (04/21/2008)
Birth Date: Dec 21, 2007 (12/21/2007). Current Age: 0 year/s, 4 month/s and 0 week/s

Age	0-4 weeks	1-3 months	3-6 months			6-12 months	12-15 months	15-18 months		18-24 months	3-4 years	4-6 years	Tally				
Rec. Date (mm/dd/yy)	12/21/07	02/21/08	Today 04/21/08	05/19/08	06/02/08	06/16/08	07/14/08	12/15/08	01/12/09	03/09/09	03/13/09	04/10/09	06/19/09	11/20/09	12/12/11	12/13/13	
HepB	AD	AD			PD												3/3
Rota																	0/3
DTaP		AD	CD	PD			PD								OD		5/5
Hib		AD	CD	PD			OD										4/4
PCV		AD	CD	PD			OD										4/4
IPV			CD	CD		OD	PD										4/4
MMR							OD	PD									2/2
Var							OD	PD									2/2
HepA							OD			OD							2/2

AD - Administered Dose CD - Catch-up Dose OD - On-time Dose PD - Preemptive Dose

Case 1: A 4 month old child who has received *HepB* at birth and one each of *HepB*, *DTaP*, *Hib*, and *PCV* at 2 months of age.

Case 2: A one year old child without any vaccination.

Figures 3-6 display the different solutions obtained for each of the two scenarios. The first two rows of each chart displays the age and dates for scheduled visits. The first column corresponds to the vaccine line-up. Each box in the chart represents four possible outcomes for a scheduled dose:

AD – an already Administered Dose,

CD – a Catch-up Dose scheduled after the recommended age,

OD – an On-time Dose scheduled during the recommended age, and

PD – a Preemptive Dose scheduled before the recommended age.

At the end of each row we give a tally of doses administered/scheduled out of the total recommended for a vaccination series to be considered completed.

Consider the solution obtained for Case 1 shown in Figure 3. Note that the *Rota* vaccine has been skipped altogether since this vaccination series must be started by 12 weeks of age and no doses can be administered after 32 weeks. Note also that although this child is 4 months behind for 5 of the 9 vaccines, the schedule has the child catch-up for all but *Rota* by

Figure 5 A catch-up schedule constructed for Case 2.

Schedule generated for: ***** on Apr 21, 2008 (04/21/2008)
 Birth Date: Apr 21, 2007 (04/21/2007). Current Age: 1 year/s, 0 month/s and 0 week/s

Age	6-12 months			12-15 months			15-18 months		18-24 months		3-4 years	4-6 years	
Rec. Date (mm/dd/yy)	Today 04/21/08	05/19/08	06/16/08	07/12/08	08/11/08	10/18/08	12/15/08	03/21/09	04/16/11	04/13/13	Tally		
HepB	CD	CD			OD						3/3		
Rota											0/3		
DTaP	CD	CD	CD				CD		OD		5/5		
Hib	CD		CD								2/4		
PCV	CD		CD								2/4		
IPV	CD	CD	OD						OD		4/4		
MMR	OD								OD		2/2		
Var	OD								OD		2/2		
HepA	OD					OD					2/2		

AD - Administered Dose CD - Catch-up Dose OD - On-time Dose PD - Preemptive Dose

Figure 6 A catch-up schedule constructed for Case 2 when limiting the number of simultaneous administrations to 4 vaccines.

Schedule generated for: ***** on Apr 21, 2008 (04/21/2008)
 Birth Date: Apr 21, 2007 (04/21/2007). Current Age: 1 year/s, 0 month/s and 0 week/s

Age	6-12 months			12-15 months			15-18 months		18-24 months		3-4 years	4-6 years		
Rec. Date (mm/dd/yy)	Today 04/21/08	04/28/08	05/19/08	06/02/08	06/16/08	07/12/08	08/25/08	10/18/08	11/03/08	12/15/08	03/21/09	04/16/11	04/13/13	Tally
HepB		CD		CD			OD							3/3
Rota														0/3
DTaP	CD		CD		CD					CD		OD		5/5
Hib	CD				CD									2/4
PCV	CD				CD									2/4
IPV	CD		CD		OD							OD		4/4
MMR		OD										OD		2/2
Var		OD										OD		2/2
HepA		OD							OD					2/2

AD - Administered Dose CD - Catch-up Dose OD - On-time Dose PD - Preemptive Dose

6 months of age. This is indicated by the trailing OD boxes at 6 months of age. Observe that once a child has caught-up, we are able to offer a range of valid dates for administration of the remaining doses as in the original recommended schedule given in Figure 1.

The solution show in Figure 4 is also for Case 1, except this time an accelerated schedule is constructed. Observe that the third doses of HepB, DTaP, Hib and PCV along with the final doses of IPV, MMR and Var have all been brought forward. However, due to the required spacing, fewer doses could be aligned during future visits and thus, additional visits are required to complete the vaccination series

in the accelerated schedule compared to the regular schedule given in Figure 3. In practice, a provider might use the information provided by the accelerated schedule to check all vaccines that can be administered on the current day and then construct a regular schedule for administration of future doses.

The final two solutions (Figures 5 and 6) display the solution for Case 3 which is often the standard scenario for internationally adopted or immigrant children presumed not to have received any vaccinations (see Cohen and Veenstra (2006)). Since the one year old child is assumed not to have received any vaccinations, the standard recommendation as displayed in

Figure 5 is to vaccinate the child with all 8 vaccines that can be feasibly administered on the current day. However, unless a clinic has many of these in combination, it is unlikely that they would actually administer 8 shots during a single visit. Figure 6 displays the solution when the user chooses to restrict the maximum number of simultaneous administrations to 4. Note how the scheduler has chosen to push back the first doses of *HepB*, *MMR*, *Var* and *HepA*. Since *HepB*, *DTaP*, *Hib* and *PCV* are long overdue priority is given to these vaccines over *MMR*, *Var*, and *HepA*. Note that when a range of possible dates is given for administering some dose, we assume the child will receive the dose on the first day in the recommended interval for the purposes of restricting the number of simultaneous administrations.

7. The Scheduler in Practice

The tool was downloaded over 7,000 times from CDC’s website in its first month of release to the public and continues to be downloaded at a rate over 1,500 per week. The tool has also been featured in over 50 different online magazines and new articles including the Washington Post (Kritz (2008)), U.S. News (Shute (2008)), and was recently featured on the front page of AAP News (Cash (2008)).

Several physicians including Dr. Bocchini (chair of the AAP Committee on Infectious Diseases) and Dr. Robert Harrison (Children’s Healthcare of Atlanta) who have used the tool have commented that in a busy office they appreciate the rapidity with which decisions can be made by using the tool when a child falls behind on his or her immunizations. They noticed that parents have brought the schedule with them to physician visits and are able to ask appropriate questions and feel they are part of the process. The amount of time saved in determining what vaccines need to be administered when a child is behind and the confidence that the recommended vaccines are administered are major benefits to them. Moreover, physicians feel that the scheduler helps them ensure that children receive vaccines within the recommended guidelines.

Feedback from parents have also been very positive. Parents have benefitted from using the tool by understanding the complexity of the immunization schedule and the importance of keeping their children up to date with their immunizations. When children fall behind on their immunizations, the tool has provided an opportunity to know what immunizations are recommended on physician visit days and what immunizations will be given during future visits. Parents have stated that they appreciate being part of the immunization process by becoming educated and able to discuss vaccine issues with their child’s physicians and nurses. Parents also like to be able to print their child’s personalized schedule of the recommended dates to administer future vaccines.

8. Conclusions

Although there have been significant improvements in infection and mortality rates for vaccine preventable diseases since vaccines were first licensed for recommended use, tens of thousands of children in the United States still contract and many die from vaccine preventable diseases each year (Roush et al. (2007)). Furthermore, given the enormous direct and indirect cost on society of not immunizing children, and the fact that many children fall behind and might not receive the optimal protection against vaccine preventable diseases, the possible socioeconomic and health benefits from ensuring the timely and accurate administration of vaccines could be significant.

Health care providers are faced on a daily basis with the challenging task of constructing catch-up schedules for childhood immunization. The manual process of constructing such schedules is both difficult and time consuming often resulting in inaccurate or incomplete schedules that can have a detrimental impact on the timeliness of coverage rates.

In this paper, we examine the complicating characteristics of the catch-up scheduling problem and design a DP algorithm that constructs a schedule for a child based on their vaccination history and current age that are optimal with respect to the potential coverage provided to the child. By observing and exploiting the

fact that the separation required between doses of the same vaccine is non-decreasing in the age some previous dose is administered, we derive dominance criteria that are sufficiently tight in practice to solve practically sized problems very quickly.

The tool is currently available for download from CDC’s website (www.cdc.gov/vaccines/scheduler/catchup.htm) and is being advocated by both the CDC and AAP as a means of encouraging caretakers and providers to take a more proactive role in ensuring timely vaccination coverage of children under their care, and ensuring the accuracy and quality of a catch-up regime.

Acknowledgments

The authors are grateful to Cathy Hogan and Shilpa Kottakapu from the Centers for Disease Control and Prevention for their assistance in part of the implementation and the dissemination of the tool.

Appendix. Validity of Dominance Criteria

Proof of Proposition 4. Let s'_2 be a feasible extension of schedule s_2 . We show that we can use s'_2 to construct a feasible extension of s_1 that is at least as good as s'_2 .

Let s'_1 be the schedule obtained from extending s_1 by scheduling for each vaccine $v \in V$, doses $i \in \{n_v(s_1) + 1, \dots, n_v(s'_2)\}$ at age $t_{v,i}(s'_2)$. We first show that s'_1 is feasible.

Clearly, since s_1 and s'_2 are feasible, s'_1 must be feasible for the age window for each dose of each vaccine.

Again, since s_1 and s'_2 are feasible, s'_1 must clearly be feasible for the spacing between any pair of doses i and j of some vaccine v when $i, j \in \{1, \dots, n_v(s_1)\}$ or $i, j \in \{n_v(s_1) + 1, \dots, n_v(s'_1)\}$. We next show that spacing is also feasible when $i \in \{1, \dots, n_v(s_1)\}$ and $j \in \{n_v(s_1) + 1, \dots, n_v(s'_1)\}$. If $i > n_v(s_2)$, then since $t(s_1) = t(s_2)$, i cannot be scheduled earlier in s'_2 than in s'_1 . Similarly, if $(v, i) \in \Psi(s_1)$ and $i \in \{1, \dots, n_v(s_2)\}$, then from condition **D-3** it again follows that i cannot be scheduled earlier in s'_2 than in s'_1 . Thus, in both cases, since j is scheduled at the same age in s'_1 and s'_2 , and since we assume the minimum gap

required is non-decreasing in the age dose i is given, the spacing between the administration times of doses i and j must be feasible in s'_1 if it is feasible in s'_2 . Hence, we may assume that $(v, i) \notin \Psi(s_1)$. If $(v, i) \notin \Psi(s_1)$, then by definition of $\Psi(s_1)$, we must have $t_{v,i}(s_1) + t_{v,i,j}^{gap}(t_{v,i}(s_1), t') \leq t'$ for all $t' \geq t(s_1)$ and thus, $t_{v,i}(s'_1) + t_{v,i,j}^{gap}(t_{v,i}(s'_1), t_{v,j}(s'_1)) \leq t_{v,j}(s'_1)$ since $t_{v,i}(s'_1) = t_{v,i}(s_1)$ and $t_{v,j}(s'_1) \geq t(s_1)$. Hence, the gap between doses i and j must again be feasible. We next show that s'_1 is feasible for the spacing between live vaccines as well.

As with the spacing of doses of the same vaccine, since s_1 and s'_2 are feasible, s'_1 must also be feasible for the spacing between any two doses i and j of live vaccines v and w respectively when $i \in \{1, \dots, n_v(s_1)\}$ and $j \in \{1, \dots, n_w(s_1)\}$, or $i \in \{n_v(s_1) + 1, \dots, n_v(s'_1)\}$ and $j \in \{n_w(s_1) + 1, \dots, n_w(s'_1)\}$. We next show that the spacing is also feasible when $i \in \{1, \dots, n_v(s_1)\}$ and $j \in \{n_w(s_1) + 1, \dots, n_w(s'_1)\}$. Indeed, if $(v, i) \notin \Psi(s_1)$, then it follows from definition of $\Psi(s_1)$ that $t_{v,i}(s_1) + t^{live} \leq t(s_1)$. Thus, since $t_{w,j}(s'_1) > t(s_1)$, it follows that $t_{w,j}(s'_1) - t_{v,i}(s_1) \geq t^{live}$. Hence, we may assume $(v, i) \in \Psi(s_1)$ and thus since $t_{v,i}(s_1) < t_{v,n_v(s_1)}$ also $(v, n_v(s_1)) \in \Psi(s_1)$. In this case, we have from condition **D-2** that $n_v(s_1) = n_v(s_2)$ and thus, from condition **D-3** that $t_{v,i}(s_1) \leq t_{v,i}(s_2)$. By construction of s'_1 , we have $t_{w,j}(s'_1) = t_{w,j}(s'_2)$, and thus s'_1 must be feasible with respect to the spacing between doses i and j of live vaccines v and w if s'_2 is feasible.

As a final note on the feasibility of s'_1 , observe that by construction of s'_1 , s'_1 has at most the same number of doses scheduled as s'_2 after age t . Thus, since s_1 and s'_2 are feasible, s'_1 does not violate the maximum number of allowable vaccinations at any age.

We next show that s'_1 is at least as good as s'_2 . Indeed, observe that by condition **D-1** and construction of s'_1 , s'_1 has at least the same number of doses scheduled than s'_2 for each vaccine. Thus, $c(s'_1) \geq c(s'_2)$ and $n(s'_1) \geq n(s'_2)$. Furthermore, if $n(s'_1) = n(s'_2)$, then $n_v(s'_1) = n_v(s'_2)$ for all $v \in V$. Thus, any dose scheduled in s_1 but not in s_2 is scheduled at a later age in s'_2 and thus we have $\sum_{v \in V} \sum_{i=n_v(s_2)+1}^{n_v(s_1)} d_{v,i}(s'_1) \leq \sum_{v \in V} \sum_{i=n_v(s_2)+1}^{n_v(s_1)} d_{v,i}(s'_2)$. In addition, by construction of s'_1 , the timing of doses scheduled in s'_1 but not in s_1 is the same as in s'_2

and thus we have $\sum_{v \in V} \sum_{i=n_v(s_1)+1}^{n_v(s'_1)} d_{v,i}(s'_1) = \sum_{v \in V} \sum_{i=n_v(s_1)+1}^{n_v(s'_1)} d_{v,i}(s'_2)$. Finally, from condition **D-4**, it follows that $\sum_{v \in V} \sum_{i=1}^{n_v(s_2)} d_{v,i}(s'_1) \leq \sum_{v \in V} \sum_{i=1}^{n_v(s_2)} d_{v,i}(s'_2)$ and thus, $d(s'_1) \leq d(s'_2)$. \square

References

- Atkinson, W.L., L.K. Pickering, B. Schwartz, B.G. Weniger, J.K. Iskander, J.C. Watson. 2006. General recommendations on immunization. *Morbidity and Mortality Weekly Report* **55**.
- Brucker, P. 2004. *Scheduling Algorithms*. 4th ed. Springer.
- Brucker, P., J. Hurink, W. Kubiak. 1999. Scheduling identical jobs with chain precedence constraints on two uniform machines. *Mathematical Methods of Operations Research* **49**(2) 211–219.
- Cash, S. 2008. Online scheduler keeps track of missed immunizations. *AAP News* **29**(7).
- CDC. 2008a. *Immunization Information Systems*. Department of Health and Human Services, National Center for Immunization and Respiratory Diseases, United States. URL: www.cdc.gov/vaccines/programs/iis.
- CDC. 2008b. *The National Immunization Survey*. Department of Health and Human Services, National Center for Health Statistics, United States. URL: www.cdc.gov/nis.
- CDC. 2008c. *Recommended schedules and guidelines for catch-up scheduling*. Department of Health and Human Services, National Center for Immunization and Respiratory Diseases, United States. URL: www.cdc.gov/vaccines/recs/schedules/.
- Chretienne, P., E.G.Jr. Coffman, J.K. Lenstra, Z. Liu. 1995. *Scheduling Theory and its Applications*. John Wiley & Sons.
- Chu, C., J-M. Proth. 1994. Single machine scheduling with chain structured precedence constraints and minimal and maximal separation times. Tech. Rep. 2268, SAGEP (INRIA Lorraine).
- Cohen, A.L., D. Veenstra. 2006. Economic analysis of prevaccination serotesting compared with presumptive immunization for polio, diphtheria, and tetanus in internationally adopted and immigrant infants. *Pediatrics* **117**(5) 1650–1655.
- Cohen, N.J., D.S. Lauderdale, P.B. Shete, J.B. Seal, R.S. Daum. 2003. Physician knowledge of catch-up regimens and contraindications for childhood immunizations. *Pediatrics* **111** 925–932.
- Drora, M., W. Kubiak, P. Dell’Olmo. 1997. Scheduling chains to minimize mean flow time. *Information Processing Letters* **61**(6) 297–301.
- Garey, M.R., D.S. Johnson. 1979. *Computers and Intractability: A Guide to the Theory of NP-Completeness*. W.H. Freeman.
- Holt, E., B. Guyer, N. Hughart, V. Keane, P. Vivier, A. Ross, D. Strobino. 1996. The contribution of missed opportunities to childhood underimmunization in baltimore. *Pediatrics* **97**.
- Irigoyen, M., S. Findley, P. LaRussa, S. Chen, P. Sternfels, L. Cooper, A. Caesar, M. Ewing. 2003. Impact of immunization schedule changes on missed opportunities for vaccination. The 37th National Immunization Conference Chicago, IL.
- Jansen, K., G.J. Woeginger, Z. Yu. 1995. UET-scheduling with chain-type precedence constraints. *Computers and Operations Research* **22**(9) 915–920.
- Kritz, F.L. 2008. For parents, an easier way to track vaccines. *The Washington Post, Health* (July 15, 2008).
- Kubiak, W., J. Blazewicz, M. Dror, Katoh N., H. Rock. 1998. Resource constrained chain scheduling of uet jobs on two machines. *Operations Research* **46**(5) 742–746.
- Luman, E.T., M.M. McCauley, S. Stokley, S.Y. Chu, L.K. Pickering. 2002. Timeliness of childhood immunizations. *American Journal of Preventive Medicine* **110**.
- Maciosek, M.V., A.B. Coffield, N.M. Edwards, T.J. Flottemesch, M.J. Goodman, L.I. Solberg. 2006. Priorities among effective clinical preventive services: Results of a systematic review and analysis. *American Journal of Preventive Medicine* **31** 52–61.
- Miller, P.L. 1997. Tools for immunization guidelines knowledge maintenance: Automated generation of the logic “kernel” for immunization forecasting. *Computers and Biomedical Research* **31**.
- Miller, P.L., S.J. Frawley, C. Brandt, F.G. Sayward. 1997. A prototype web site for immunization knowledge maintenance. *Proceedings AMIA Annual Fall Symposium* 293–297.

- Pinedo, M. 2002. *Scheduling: Theory, Algorithms, and Systems*. 2nd ed. Prentice Hall.
- Plotkin, S.A., W.A. Orenstein. 2004. *Vaccines*. 4th ed. Elsevier Health.
- Rasulnia, B., J. Kelly. 2006. Immunization information systems progress - united states 2005. *Morbidity and Mortality Weekly Report* **55**(49).
- Roush, S.W., T.V. Murphy, the Vaccine-Preventable Disease Table Working Group. 2007. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the united states. *The Journal of the American Medical Association* **298**(18).
- Shute, N. 2008. A new tool to manage your child's vaccine schedule. *U.S. News and World Report, Online* (May 27, 2008).
- Szilagyi, P.G., L.E. Rodewald, S.G. Humiston, R.F. Raubertas, L.A. Cove, C.B. Doane, P.H. Lind, M.S. Tobin, K.L. Roghmann, C.B. Hall. 1993. Missed opportunities for childhood vaccination in office practices and the effect on vaccination status. *Pediatrics* **91**.
- Wikum, E.D., D.C. Llewellyn, G.L. Nemhauser. 1994. One-machine generalized precedence constrained scheduling problems. *Operations Research Letters* **16** 87–99.
- Zhou, F., J. Santoli, M.L. Messonnier, H.R. Yusuf, A. Shefer, S.Y. Chu, L. Rodewald, R. Harpaz. 2005. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the united states, 2001. *Archives of Pediatrics and Adolescent Medicine* **159** 1136–1144.