Pediatric Immunization Planning Using a Project Control Comprehensive Framework: A Software Development

Abstract

Pediatric immunization scheduling problem (PISP) plays a crucial role in both national cost savings and public health planning. To improve pediatrics immunization and to help insiders, Iran University of Science and Technology (IUST) collaborated with Shiraz University of Medical Sciences (SUMS) to develop a decision support tool for creating optimal catch-up schedules individualized for children 0 to 6 years old vaccination. To schedule an appropriate vaccination catch-up plan, due to need for including of too many factors like vaccination history and age, is a complex and lingering procedure for the insiders. To deal with this problem, we presented a novel planning approach considering logical similarities held between PISP and the resource-constrained project scheduling problem (RCPSP). Our solution is a comprehensive framework, which comprises of four steps; (1) a project control sight on the PISP and discussion the similarities. (2) a Mixed Integer Programming (MIP) approach, which deals with baseline planning as a combination of three RCPSP models. (3) Providing a user-friendly decision support tool based on a proactive project control dealing with dose(s) missed from the recommended plan and (4) a project-based technique for cost and quality evaluations. As the results of a pilot implementation in Allergic Research center (ARC) of SUMS shows, the proposed tool was successful to gain clinicians' satisfaction. Moreover, these results show $ 15,000 cost saving per child in approximate cost evaluations.

Keywords: Pediatric Immunization, Project Planning, Catch-up Scheduling, Earned value Management, Decision Support Systems, Public Health, Healthcare Solutions

1. Introduction

Healthcare issues, especially those concern immunization has always been economically and socially important [1]. The pediatric immunization problem gained attentions to itself as a fundamental issue for each nationwide healthcare system. In addition, it has significant impacts on public health and can be considered as one of the most cost effective preventing actions to take [1, 2]. Every five or more years, a new recommended immunization schedule is established. Some considerations like recommended age of administration for each dose of each vaccine and also minimum age of this administration is established (see Figure 1) along with a catch-up plan recommendation (see Figure 2).

Vaccine>>	Iran National Recommended Pediatrics Immunization Schedule												
BCG	BCG												
DTP			DTP	at least 1 m*	DTP	at least 1 m*	DTP	at least 1 m*			DTP	at least 1 m*	DTP
OPV	OPV	at least 1 m*	OPV	at least 1 m*	OPV	at least 1 m*	OPV	at least 1 m*			OPV	at least 1 m*	OPV
MMR									MMR	at least 1 m*	MMR		
Hep.B	Hep.B	at least 1 m*	Hep.B	at least 2 m*			Hep.B						
month >>	Birth	1	2	3	4	5	6	…	12	…	18	…	72

*m= month

Figure 1. National recommended immunization schedule

Even it may seems that missing in up-to-date vaccination would not be significantly effective, it is considerable in the age-appropriate vaccination [3]. However, assessing the timeliness of coverage for immunization is necessary even in up-to-date vaccination coverage [4]. Moreover, providing an appropriate catch-up plan can be granted as a crucial health issue when there is less than 30% (1.83 plan of highest possible of 6) possibility of providing a correct optimal catch-up plan manually by health insiders [5]. Based on some statics, children mostly do not receive the appropriate catch-up plan, until the age of getting to school, which can result in less vaccine coverage for them [6]. In Iran, despite high development from 55% to 96% immunization coverage rates achieved in recent years, there still remains some concerns on immigrants and outskirts residents about vaccination coverage [7, 8]. This raises concerns when there still remain vast masses of immigrants and low socioeconomic level population without being considered in such surveys [9]. This unknown part of Iran population get 54% to 93% of its pediatric immunization out of time. Thus, as another immunization performance index, timeliness has to be developed, especially among outskirts areas and non-Iranian population [10-12].

Vaccine>>	Iran National Recommended Pediatrics Immunization Catch-up guideline								
BCG	BCG								
DTP	DTP	at least 1 m* (if the interval is more than 4 years, then no more doses are needed)	DTP	at least 1 m*	DTP	at least 6 m*	DTP		DTP
OPV	OPV	at least 1 m* (if the interval is more than 4 years, then no more doses are needed)	OPV	at least 1 m*	OPV	at least 6 m*	OPV		OPV
MMR	MMR	at least 1 m*	MMR						
Hep.B	Hep.B	at least 1 m* (if child received the first dose before 18 m)	Hep.B	at least 2 m*			Hep.B		
M after FV**	FV**	1	2	3	4	…	10 to 16	…	6 YO***

*m= month
*FV= First Visit
***YO= Years Old

Figure 2. Catch-up guideline for national immunization plan

To help caretakers, practitioners and individuals, we developed a decision support tool that comprises of an easy-to-use user interface, which is being handled by a proactive algorithm. This tool is presented through a comprehensive framework, which is based on project control and management tools. It is proposed to address the PISP Through a comprehensive framework, in four harmonic steps; first, we discuss so many common attributes in both PISP and project problems (see Figure 3). Then, in the second step, a linear mathematical model based on project planning approaches – so called Resource Constraint Project Scheduling Problem (RCPSP) - is introduced to address the problem of new vaccine series introduction and baseline (recommended) planning. With the goal of real-life implementations and to deal with dose(s) missing, in the third step the individualized decision support tool is designed using Visual Basic (VB) programming language to develop a proactive algorithm for catch-up schedules presentations. The last step of the framework introduces a performance monitoring technique; Earned Value Management (EVM), which provides the opportunity to have a quantitative sense of immunization losses in monetary terms.

RCPSP attributes

- **Problem**: GPR/QTS in R&D projects
- Sub projects
- Tasks
- Tasks' finish
- Quality of execution
- Objectives:
  Least make span
  Highest possible quality

PISP attributes

- **Problem**: PISP
- Vaccine series
- Doses
- Administration of doses
- Deviation from recommended time
- Objective:
  administration before school
  optimum administrated doses

Figure 3. Similarities between PISP and a project control problem

Based on best of our knowledge, there is just few works on providing immunization decision tools. In Millers et al works the tool is designed just for two-dose vaccine series and needs so many adjustments even after little changes in the recommendations and/or considerations [13, 14]. In a newer work, Smalley et al presented a very good tool on the basis of dynamic programming [15]. This tool needs no further adjustments for such changes but it has no quantitative evaluations of losses in quality of catch-up plans. In next sections we present a tool, which is designed based on project control techniques to solve the PISP. This tool has been used and verified by caretakers and practitioners of SUMS. Moreover, quantitative evaluations of the presented catch-up plan is another unique attribute of the presented tool.

2. Related works

Some researches like Engineer et al. [6] has suggested a Dynamic Programming (DP) approach to deal with pediatric immunization problem and Abrahams and Ragsdale [16] presented a decision support tool for travel vaccines administration using linear programming (LP) and Genetic Algorithm (GA). There is other works which try to provide solution approaches for healthcare problems with introducing decision support tools [17-19]. To review related works, first we review some important works on vaccination, especially operations research (OR) applications on health care delivery. After that, Considering the main contribution of this paper, we tried to see PISP as a combination of three RCPSP problems. Therefore, we briefly review the RCPSP models, especially the ones with considerations of time intervals and quality of execution to satisfy PISP's attributes (see Figure 3). Then, a brief introduction of EVM will be presented. Finally, we compare and contrast the presented work to those of past and highlight its advantages.

Children healthcare delivery

Pertaining to health care delivery, researchers have done so many investigations on macro decision making and strategies of vaccination to make the best choice before or during outbreaks, considering population's attributes [20-29]. A vast mass of works on vaccination focused on the strategic decision level and tactical level still needs more attention. There are also some other works on healthcare problems modeling. Because of diversity in objectives, they are classified based on considering either the concept [30, 31] or mathematical modeling viewpoints [32, 33]. Some works tried to find better methods, especially for vaccination effective factors in some situations, like, when there is a catch-up scheduling to be conducted [34, 35]. Applying a recent integer programming technique and genetic algorithm in computation stage to introduce a decision support system (DSS) for travel vaccination is the result of another article [16]. researches have used mathematical models to address the question of: what is the best time/amount for immunotherapy to reduce its side effects [36, 37]. Finally, the work which inspired authors to use RCPSP modeling in pediatric immunization scheduling problem have used DP for catch-up scheduling of 0-6 year-old childhood vaccination [6] which led to a *universal* tool [15].

RCPSP models

To control a project is to decide when some activities will start and how they will consume their related resources [38]. RCPSP, as Vanhouck states, is to schedule the best start and finish times for activities in a project considering the precedence relationships between them and resource availability aiming an optimum status like minimum cash flow or makespan [39]. This field has called researchers attention and has been addressed as one of the main OR application areas since then. To introduce RCPSP exact approaches and evaluate their performance, Hartman and Drexel did a valuable work on clustering these models [40]. Given the concentration of this paper, a good classification has been done by De Reyck et al. 1999 [41] to classify RCPSP-GPR (Generalized Precedence Relations) works. Moreover, there are some works concentrating on the exact procedures to solve RCPSP-GPR all of which made use of the GPR for time slots presented by Bartusch et al. [42].

Most of the time, linear modelling approaches have used binary variables, which is the main reason why the RCPSP is prone to be a NP-hard problem. Pritsker et al. introduce a binary variable; X_{it} which is 1 when activity i finishes at time t [43]. This model has at most nT variables and $O(n^2+mT)$ restrictions [44]. Kaplan and Klein, each introduces a different way of formulation [45, 46]. However, in both works, the binary X_{it} is 1 when activity i is in progress at time instance t, which makes nT variables and $O(n^2T)$ restrictions, that exceeds those of Pritsker et al. model. Derived from Pritsker et al. work, Talbot introduces a model to deal with multi-mode RCPSPP (MRCPSP) [47] and MRCPSP-GPR is derived from Talbot's work [48]. In the last two works, in contrast with the Pritsker et al , X_{it} deals with the start of activity i in t. In addition, two other modeling views are introduced in the literature. In the first by Alvarez Valdes (1998), $X_{ij}=1$ if activity i precedes activity j [49]. This model, in contrast with the others, can have continues time environment. The second one makes use of two binary variables; X_{it} and Y_{it} where $X_{it}=1$ when subset i processed in time t and $Y_{it}=1$ if act j finishes at time t [44].

As it will be explained later, the best-match RCPSP approach, which can properly be used as the basis for the pediatric immunization scheduling, is driven from a combination of three RCPSP models. The First model is the MRCPSP-GPR with unlimited resources, which is denounced by $PS\infty|temp|C_{max}$ [50]. The MRCPSP-GPR first formulated by Talbot [47] and De Reyck and Herroelen present a heuristic solution approach for that [48]. The second RCPSP model is resource constrained project scheduling problem with quality dependent time slots (RCPSPQTS) which is introduced by Vanhouck [39, 51]. Finally, the third inspiring project problem, which shares so many implementation similarities with RCPSPQTS, is RCPSP in Research and Development (R&D) projects. Activities in this projects are always prone to have some sort of uncertainty in the output quality. Such uncertainties usually raise when a new product is to be produced in a regular manufacturing environment [52-54] or new pipelines are to be constructed [55-58].

Earned value management

Some of previews works have educated vaccination costs in other countries like Germany and Netherlands [59, 60]. Having the project controlling insight in mind, we tred Earned Value Management (EVM) technique for this issue. This concept led to create a powerful procedure which helps the scope, makespan and resource consumption of a project to be quantitatively controlled [61]. With this managerial technique, getting a feedback of the current project's status, predicting its future status and controlling both current and future status will be accesable [62]. We need to introduce three indices of EVM. The first one is Budgeted Cost of Work Performed (BCWP), which represents costs of the project if it follows, exactly, the initial plan. The second one, Actual Cost of Work Performed (ACWP), is calculated at the status date, the date on which a report about project's situation is needed (the date we compare planned and actual progress of the vaccination). This report is based on what has been done really in the execution step until now (status date). The third and final index is the Cost Variant (CV) which is positive, if BCWP>ACWP and negative otherwise (eq. 1) [61].

Figure 4 represents the three aforementioned indices and their relationships. It is important to mention that the relevant costs is considered based on either loses in immunization quality (and its health outcomes) or economic implications of postponing (or cancelling) the recommended dates of doses administration. We will discuss the usefulness of EVM technique and its harmony with the comprehensive framework.

$$CV = BCWP - ACWP \qquad (1)$$

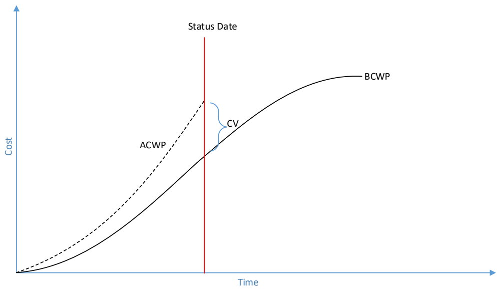

Figure 4. EVM indices to evaluate project status

Deviation from previews work

The Pediatric immunization baseline linear model is inspired from two RCPSPs: MRCPSP-GPR [48], RCPSPQTS [39]. Also, the proactive project scheduling environment of PISP, is same as what is explained in Choi et al. work with R&D attributes [55]. We will present a simple linear model for presentation of the baseline (recommended) immunization plan. Then, a decision support tool based on proactive project control approaches is presented, which can fill the gap of quantitative evaluation of catch-up plans.

3. Problem description and solution approach

To provide a good immunization catch-up solution, the best vaccine coverage and timeliness have to be met simultaneously [9-12, 63]. This procedure has to be done for each individual newborn, who, by any reason, missed some doses of the recommended (baseline) immunization schedule considering his/her vaccination history and age. Each administration is allowed unless it is infeasible or contraindicated [15]. For instance, when more than 4 years is passed after the last administration of DTP, then as the contraindication terms goes, no more than one *reminder dose* is needed to be planned for administration for DTP vaccine series. There are some minimum and maximum ages for each doses of each vaccine. The catch-up plans must not violate these limitations for each dose, again based on clinical considerations. Moreover, child's comfort is an important factor, which can put some limitations on maximum doses allowed to be administered during each visit.

Caretakers and practitioners face such complexity every day and for each child. Moreover, there is a vague understanding of implication costs and possible losses of the catch-up planning. pondering so many similarities between projects and PISP, we provided a comprehensive framework to help caretakers in catch-up decision makings and health the authority to have a quantitative outlook of catch-up planning inevitable costs. Our framework has to be useful in further macro-scale immunization applications like vials production supply chain and public health cost evaluations (see Figure 5).

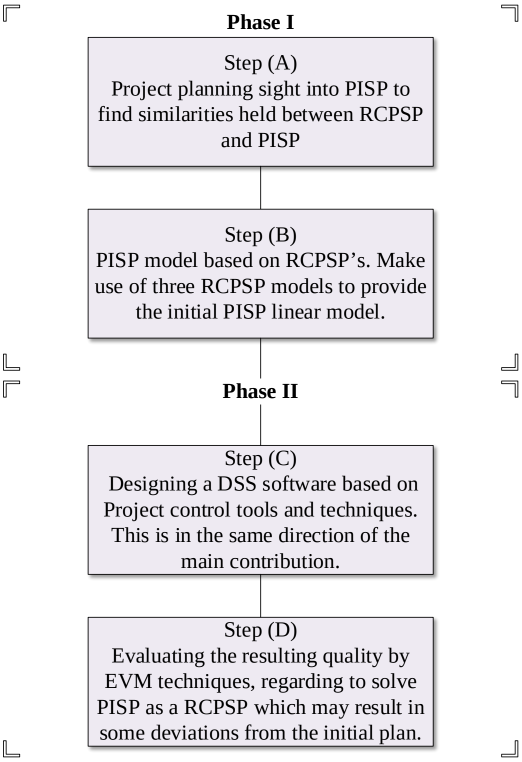

Figure 5. The comprehensive Framework of project controlling sight on PISP

The presented tool has to meet some criteria. It has to be fast, user-friendly, provide practitioners some situational changes in roles and make quantitative and monetary evaluations available. For the two first criteria, we designed a graphical user interface for our tool, which can make a very fast interaction with the proactive algorithm of the tool and make the procedure of getting the catch-up plan very short. As the proactive project controlling matches with the PISP catch-up planning issue, we have made some interactive attributes for caretakers, who feel some changes in vaccines priority would be beneficial. Finally, as the result of proactive project controlling environment and EVM indices, our tools can give quantitative evaluations and costs analysis of the catch –up plan, considering it with the recommended (baseline).

PISP tool

In this section, we introduce the PISP tool and the challenges we faced along with the solutions we brought for each of the challenges. More discussion on these proactive project-based approaches is discussed in the appendix (see step c of the framework in the Appendix). Our tool, which is designed based on proactive project scheduling methods, comprises of two parts; a Graphical User Interface (GUI) and a Proactive Scheduling Part (PSP). It can also provide an individualized initial plan for the newborns, based on their date of birth (see Figure 6).

Figure 6. Getting the individualized recommendeation immunization schedule based on date of birth

To initiate for a catch-up schedule, entering birthday date is necessary as well (see Figure 7). After the birthday is set, vaccination history data is needed to be added through another window (see Figure 8). During developing this tool, there were some similarities in proactive project controlling method, which made the development process so much easier and asserted the assumption of considering the PISP as a project controlling problem (see step c of the framework in the appendix).

Figure 7. Inserting the birthday date for the child, whoc needs an individualzed catch-up plan

However, there existed some challenges in PISP. For instance, the tool had to be able to consider it, if child comfort was needed and make sure that limitation on maximum doses in each visit is met. Moreover, the recommended time window for each dose administration must not be violated. For each dose of each vaccine, there is a minimum and maximum age for administration, during which that dose has to be scheduled for administration.

Figure 8. The panel for entering child's vaccination history and practitioner possible intervention in changing vaccines' priority

Sometimes, based on child's clinical situation, it may be necessary to make changes on vaccine series priority. For example, the practitioner may think that some doses are needed to be scheduled earlier than what is recommended in the catch-up guideline schedule (Figure 2). In such situations, the practitioner can make some changes in recommended vaccines priority order and make one or more vaccine type crucial with the highest priority (see Figure 8). This change would be necessary to reduce the risk of contracting some diseases, for which child has not received any doses.

Figure 9. After providing the catch-up plan, a new window will open asking about the name and location of catch-up data plan in .xlsx (Excel readable) format

Catch-up plans can be available in .xlsx format, which is readable and easy-to-use in Microsoft Excel. Practitioners and other users can print these plans and give them to children parents. Moreover, it can be archived in clinical databases for future follow-ups and evaluations on how precisely the plans are being followed.

4. Practice at the allergy research center

We have used the project-based tool in Allergy Research Center (ARC) and Department of Pediatrics, Shiraz University of Medical Sciences (SUMS) on 10 children with some missing in their received vaccines. To make the numbers more reasonable, we used international drug price indicator 2014 Edition [64].

Vaccine Name	price (USD/Dose)
BCG	0.15
Polio	0.25
Rotavirus	6.96
Hep.B	7.6
DTP	0.55
MMR	0.23

Because some of the vaccines are different or is a combination of more than one vaccines, the average cost per dose will be driven from Table 1. prices for some vaccines. Therefore, the cost per dose for vaccine series will be 2.62 $/Dose for all vaccines series (cost per hour for resource in project variable costs). We add 30% as overhead costs comprising later treatment costs, facing with outbreaks and the like (see below equation).

$$Cost\ \left(Dollar\right)\ /\ Dose\ for\ all\ vaccine\ series\ =\ 2.62\ \times\ 1.3\ =\ 3.4\ \$\ /\ Dose \qquad (2)$$

All vaccination history records for the 10 children is depicted in Table 2. The 10 children vaccination history came to ARC in June 16, 2016. We have ran the project-based decision support tool for each of them to get their individualized catch-up plans. We consider the child's comfort (limitation on the maximum allowed administration) in all of the 10 cases. All of the children came to the ARC in June 16, 2016.

No.	vaccines history					birth	last visit
	BCG	DTP	OPV	Hep.B	MMR		
1	0	1	1	0	1	6/12/2014	14/2/2015
2	1	0	0	1	1	5/5/2015	22/1/2016
3	1	2	2	2	1	18/6/2015	12/11/2015
4	0	0	1	1	0	2/8/2014	2/10/2014
5	1	1	1	1	1	14/1/2014	25/3/2014
6	1	1	0	0	0	1/8/2014	4/5/2015
7	0	3	2	2	1	1/2/2013	1/5/2015
8	1	2	1	1	0	11/12/2014	13/4/2015
9	1	1	1	1	1	2/8/2015	22/12/2015
10	1	1	0	1	1	19/11/2014	15/10/2015

Table 1. The 10 children vaccination history came to ARC in June 16, 2016

Project-based tool's output for the 10 children is depicted in the Table 3 below. As the table shows, considering an average cost of 3.4$ for each dose, each child's vaccination could cost approximately 1500$ to 6500$ if his/her baseline plan (BCWP) be followed. However, as all of the 10 children are having some sort of missing in their vaccination histories, it dictates some raises in the actual costs of their immunization until now (ACWP). As the result of these deviations, additional costs (CV) will be figured in the evaluations (derived from equation 1).

No.	**Tool's output**				
	finish date	**BCWP**	**ACWP**	**CV**	**Solution time in a core i5 CPU**
1	23-Mar-17	2,448.00	5,059.20	-2,611.20	4.79
2	7-Nov-17	2,448.00	18,441.60	-15,993.60	4.38
3	12-Jan-16	6,528.00	15,150.40	-8,622.40	4.16
4	20-Aug-17	1,632.00	2,937.60	-1,305.60	4.15
5	12-Jan-17	4,080.00	8,296.00	-4,216.00	3.87
6	25-Apr-18	1,632.00	12,892.80	-11,260.80	5.24
7	29-Jan-17	6,528.00	73,675.60	-67,147.60	5.03
8	7-Mar-17	4,080.00	10,852.80	-6,772.80	4.25
9	12-Jan-17	4,080.00	16,728.00	-12,648.00	4.63
10	27-Apr-17	3,264.00	30,899.20	-27,635.20	4.71
sum		36,720.00	194,933.20	-158,213.20	45.21

Table 2. The project-based tool output catch-up plans

As Table 3. The project-based tool output catch-up plans finely shows, just these 10 children's vaccination costs more the 36,000$ at least amount and until the day of their visit to the ARC in June 16, 2016, their combined immunization costs forced more than 158,000$ (CV index in tool) to the health section. This is just an estimation based on the international drugs price indicator [64]. More factors like cure costs or cost of massive outbreaks can be added to this evaluation to give a better sense of the real costs which may happen as a result of falling behind the baseline schedules.

Based on the last updates on the population, in Mamasani district, a rural district near Shiraz city, there are nearly 4689 children with less than 6 years old. If just 1% of the children in this district face some missing in their vaccination, the approximate cost of 742,600$ will be added to the nationwide costs eventually. Therefore, using this tool can be so beneficial in terms of health cost control. Furthermore, users of the tool in ARC gave very good feedbacks about the tool interface and its ease of use. The computing and resulting process also satisfied them.

5. Discussion and findings

The presented framework, as mentioned before, gives a project controlling sight on the PISP. It also eliminates the lack of linear model in immunization baseline planning. In addition, it presents a new multidisciplinary area and brings RCPSP approaches as a potential fine solution for health-related scheduling/rescheduling issues. The PISP model, despite its NP-Hard roots of the RCPSP models, does not takes too much CPU time, which means it can easily save time during the implementation comparing with the manual method which had been used before (However the model is been tested on a fast computer with a core i5 CPU). Moreover, the framework presents a decision support tool which helps vaccination insiders in many aspects (e.g. make rescheduling faster and more precise). Individualized plans then are available in case of fallings behind the recommended (initial) plan. Besides, this new look at the pediatric immunization shows a great harmony either when the similarities between PISP and RCPSP was discussed or when the steps of the framework matched comprehensively through project control perspective.

Some investigations on application of the EVM techniques on quality of the immunization was based on the core idea of the framework; using project controlling and scheduling methods and techniques in vaccination. This investigation gives a quantitative sense of the catch-up plans and the cost of missing of the previews doses. Such indices can be very useful when macro-scale decisions in immunization, like budgeting, is to be considered.

Uniqueness of the presented approach

Through using project scheduling and control techniques to address the pediatric immunization problem, we presented a comprehensive framework for the first time in another discipline rather than project planning. Then, a mathematical linear model is presented to give the pediatric immunization baseline schedule as another step of the framework. The presented mathematical model, according to the best of author's knowledge, is the first linear model to address finding the immunization's baseline plan. Again, the comprehensive framework conducted by development of a new decision support project-based tool to address the catch-up plan problems for possible missing in the vaccination. The framework is compatible with its issue (immunization) until when outcomes evaluations is to be done with EVM technique. Same as previews steps, the immunization catch-up plan effectiveness (quality) evaluation is designed using project monitoring techniques and indices, which led to making a comprehensive framework eventually.

6. Conclusion

Pediatric immunization plays a crucial role in national costs savings amongst other strategic healthcare operations planning. Time consuming process of introducing new vaccines and complexity of rescheduling a new immunization plan, which is driven from the characteristics of each vaccine series and other health-related considerations, has always needed fast and precise scheduling actions. Considering so many similarities between pediatrics vaccination planning and project controlling issues, a comprehensive framework is introduced to address children's (0-6 years old) vaccination problem. This framework comprises all the steps from beginning of the planning procedure to monitoring it and evaluating its final results, all of them using a specific project controlling tool and techniques. Three RCPSP models (MRCPSP-GPR, RCPSPQTS and RCPSP in R&Ds) where used to devise an apt initial (baseline) pediatric immunization linear model for the first time. This model sees the PISP as a project with multi-modes for execution (time of the administration) and generalized precedence relationships between the activities, which needs to minimize immunization effectiveness (quality) loses. This project's activities have some sort of uncertainties during the execution period when there exist s falling behind the baseline. Now, the previews problem changes a bit and becomes a project with uncertain activities (what is happening in the R&D projects usually). To devise an application to be used in real-life vaccination planning situations, the Project-based approach is designed and developed. This decision support tool is design to satisfy the need for providing catch-up planes fast and precise and also individualized based on child's vaccination history. It can also be used to provide the individualized baseline plans. Finally, another project controlling technique, which can make profit when be used for evaluation the quality of catch-up immunization plans, EVM was shortly reviewed and mentioned as the possible and useful approach for vaccination quality evaluations. We have mentioned and discussed three EVM indices here in this paper. However, this technique (immunization's earned value investigations) can be the basis for deeper researches in immunization cost in the further studies. The results of such researches can led to new strategic cost managements in health care sections inventory control. For instance, it can be addressed from it's supply chain points of view especially when we are facing with perishable vaccine vials. Moreover, as individualized catch-up plans are available, a good database of children vaccination history can be established. Finally, this framework has a general look on the vaccination and it can be used for other ages and target groups like pregnant immunization planning and rescheduling.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest statement

AE is a faculty member of Allergy Research Center & Department of Pediatrics, Shiraz University of medical sciences (SUMS), Shiraz, who made the pilot implementation of the presented tool easier. The presented tool also was being bought by the SUMS along with another decision support tool through a commercial contract at the time of submission of the manuscript.

Appendix

The comprehensive framework in detail

PISP and its Project control-based solution framework (step A)

We have a certain number of vaccine series all encompass of a number of doses. Each dose of every vaccine series has a recommended administration time span during which, that dose can be administrated without any lose in immunization quality (or any postponing or cancelation). In that regard, each dose is recommended to be administrated in between its recommended time window (according to the initial plan and or clinical consideration). There may exist some situations in which, one or more than one dose, cannot be administrated in their recommended time zone (for example, when parents forgot to bring their child in time of the administration date). These delays would be according to doses' conditions (in some vaccine series, intervals between doses are not the same) or the time at which some previous doses is administrated (if the interval between some doses of some vaccines is more than two years, then the precedence doses administration has to be cancelled). In this regard, sometimes, doses may need to be either rescheduled for administration or even be excluded from future schedules based on some preceding situations (e.g. when the previous dose is administrated). Having vaccination considerations in mind and according to the time of administration of each dose, certain time intervals (delay) must be passed before the preceding doses can be administrated. Sometimes, especially when the scheduled time of a dose is after the latest allowed time, successor doses of that dose do not need to be administrated anymore. In most situations, the successors must not be administrated regarding to possible medical implications. For instance, if a dose is scheduled for time unit 7 and its latest allowed time unit for administration is 5, then that dose is planned to be administrated after the authorized time unit. Here, the relative vaccine series is considered as *incomplete* and is terminated prematurely. Finally, considering children's body limitations and to avoid their significant discomfort, experts always recommend a limitation on maximum number of all doses of all vaccine series which can be administrated during one visit (at the same time unit).

PISP, as introduced here, exactly resembles the attributes of R&D projects problem. In such projects, based on the resulting quality of each activity, the execution or cancelation (excluding from the scheduling process) of successor activities is determined. These projects, most of the time, have objective functions of maximizing output quality and/or minimizing the makespan coincidently [55, 65-67]. more interestingly, these objective functions are similar to what is expected from an appropriate immunization schedule (maximizing the number of received doses within their recommended time windows and reducing possible deviations; quality of the immunization), and minimizing the whole schedule's duration (immunization's makespan). In this respect, the PISP can be modelled as a specific RCPSP, but with some more considerations. We use MRCPSP-GPR, RCPSPQTS and R&D projects' characteristics to deal with the PISP modeling issue. As Figure *10* represents, RCPSP and PISP resemble each other in many aspects.

Given the main attributes of PISP, it shares so many attributes with RCPSP. In this research, we make use of RCPSP models with a novel application: PISP. Considering the similarities (Figure *10*) we decide to make use of three RCPSP models to present a MIP approach for PISP. Figure *10* illustrates a project with two sub-project consisting of 4 and 3 activities respectively, and an immunization scheduling consists of two vaccine series each has 4 and 3 does respectively to be administrated as well.

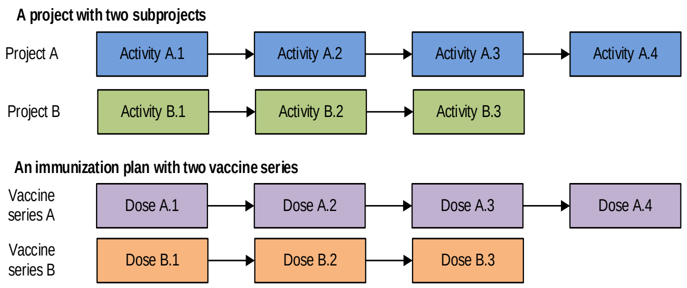

Figure 10. A simple illustration of project and immunization scheduling

Considering aforementioned attributes shared between RCPSP and PISP (Figure 3), a PISP can be dealt like a project for more evaluations and investigations (like dealing with doses as activities). Considering difficulties of using LP for catch-up vaccination scheduling problem mentioned by Engineer et al. [6], proactive project scheduling policies can be beneficial for PISP model to deal with more dynamic situations like when a child falls behind the initial(baseline) schedule. To make this happen, we make use of project control-based solutions, which have been used for project planning and scheduling as the basis for the presented vaccination DSS. Having in mind that some RCPSP models have the objective functions, which are designed to maximiz the expected received quality (RCPSPQTS for instance), some analysis in terms of the quality of received immunization can be conducted using another project control technique, EVM. All of the models, tools and techniques mentioned before, have been used for project control problems, which asserts the main contribution of project control sight on the immunization programme. Pondering PISP's similarities with RCPSP, we decided to present a comprehensive framework with a project controlling sight on PISP. This framework comprises of two phases and four steps (see Figure 5). The first step is to look at PISP as a project.

Figure 5 illustrates the procedure of implementing the RCPSP to deal with PISP through a comprehensive framework. All of the four steps contribute to the framework and is in consistency with its main idea of using RCPSP to solve PISP. In this paper, we present steps (A), (B) and (C). Step (D) will be discussed briefly and will be the main material of later investigations on macro healthcare cost evaluation and decision makings. The present paper tries to provide a simple, still practical approach within the comprehensive framework to address PISP. Literally, we have the step (A) passed by having a project planning look on PISP here.

PISP mathematical model (Step B)

Now, let us have a look on modeling children vaccination problem using the three RCPSP models attributes. To do this, first, some assumptions and notations need to be explained. Having Choi et al. R&D project's environment in mind, vaccine series are considered to be single projects, consist of a finite number of activities [55]. Here, doses of the vaccine series are considered as the projects' activities. Same as Choi et al., each dose's (activity) precedence relationship in each project only rides on it preceding dose (activity) administration (execution) time (When the precedence dose is administrated). Each dose has a period, during which it can be administrated without lost in quality. This time interval provides the highest vaccine effect (quality) and if this time intervals are violated as the result of the delays (MRCPSP-GPR's FF^{min} time lags) the vaccination effect will decrease. To avoid losing effectiveness (quality) the model is forced to schedule doses in their relevant recommended time intervals as much as possible or at least, with minimum deviation from the recommended times. To state it clearly, the more a dose is scheduled beyond its allowed time window, the less the immunization effectiveness (quality) will become. Sometimes some doses may be scheduled too late, when immunization considerations impose situations, that no more doses can be administrated and the whole vaccination series of that specific vaccine will be terminated (*incomplete*). Again, think of Choi et al.'s problem [55], in which it is possible to cancel activities based on their execution results (when result in failure). For the sack of child's comfort, it needs some limitations on the number of simultaneous administrations. It means in each time unit (we considered each time units as a four weeks period or one month) only a certain number of doses (activities) can be administrated (executed). To state more clearly, if we pretend that each dose (activity) needs one unit of renewable resource for its administration (execution), maximum allowed number of administration in time units is considered as maximum renewable resources in any time unit. This limitation is very similar to the renewable resources constraints in the MRCPSP-GPR which represented by De Reyck et al. [48]. As a result, doses of vaccination series, has no relation with the doses of other vaccination series (projects) unless in resource usage (limitation on number of administrations). There may happen some assignment deviations from the recommended time windows, which will cost some penalties in quality to the immunization considering all constraints. As Vanhouck represents this loss in RCPSPQTS, we made use of some of these constraints and also his quality based objective function later [51].

Comparing with the MRCPSP-GPR model, like Pritsker et al., X_{it} is a binary variable, which is 1 when i is finished on time unit t, so, the d_{jm} is excluded from the model, but its related attributes will be carried by X_{it} and D_{it}^{v}, which is introduced later as a time lag parameter (FF min). Same as aforementioned MRCPSP-GPR model, time units are discrete but, despite MRCPSP-GPR, according to the later introduced objective function, are considered in the whole available time span and are just restricted by the "Deadline" (here the parameter Y, which is the age of 6 when children go to school). To make the model more useable, d_{im} (in De Reyck work) is excluded from the model and D_{it}^{v} is used instead, because the execution of each dose depends on the time unit at which, the precedence dose is administrated (preceding activity is finished). More tellingly, D_{it}^{v} has the attributes of FF^{min}. For the sack of simplification we consider that the FF^{min} relation is the only type of four possible precedence relation types (FS, FF, FS, SS , all in either max or min limitation). The goal is to Maximize number of doses to administrate, which can be translated, in project terms, to as much as possible activities of the project to be done. To limit the maximum doses (activities) which can be administrated (executed) at a single time unit, a constraint is introduced as well (Max). Considering RCPSPQTS model, the PISP objective function is to minimize losses of quality in immunization terms (minimum loss in effectiveness). The problem, consists of a number of vaccine series (projects) each consist of some doses (activities) which have to be scheduled, considering delays (time lags) which are needed to be passed before the administration (execution) of the next (successor) dose of that vaccine series. The delay is determined according to administration of the previews dose (which is from the FF^{min} precedence relation type).

Sets:

V: The set for all vaccine series (sub-projects).

I^v: The set for all doses (activities) of vaccine series v.

T: The set for all time units (time here is considered as discrete units).

Parameters:

s^v_i: The earliest recommended time unit to administrate dose i of set I^v .($i \in I^v$)

f^v_i: The latest recommended time unit to administrate dose i of set I^v .($i \in I^v$)

t: The discrete time unit ($t \in T$)

Max: maximum number of doses of all kind allowed to be administrated in a time unit

Y: The deadline of finishing the whole program (all projects)

D^v_{it}: The necessary delay to be passed before dose i+1 can be administrated when dose i is administrated at discrete time unit t (FF^{min} time lag).

BQ: cost of losing quality (effectiveness) of the immunization per each time unit deviation from earliest and latest recommended administration times.

LQ: general cost of administrating doses during their recommended time units.

Variables:

x^v_{it}: The binary variable, which is equal to 1 when dose i of the series v administrated in time t, and is equal to 0 otherwise.

dev^v_i: the integer variable to denote deviation from recommended administration time.

The pediatric immunization mathematical model then is shown as below:

$$Min \sum_{i \in I^v} dev^v_i .BQ - \sum_{i \in I^v} \sum_{t \in [s^v_i, f^v_i]} x^v_{it}.LQ \qquad (3)$$

Subject To:

$$\sum_{t \in T} x^v_{i\,t} \le 1; \forall i \in I^v, I^v \in V \qquad (4)$$

$$\sum_{j > i \in I^v} x^v_{it} \le \mathrm{M}.\sum_{t \in T} x^v_{it}; \forall \mathrm{i} \in \mathrm{I}^v, \mathrm{I}^v \in V \qquad (5)$$

$$\sum_{t \in T} (t + D^v_{it}).x^v_{it} \le \sum_{t = s^v_{i+1}}^{T} t.x^v_{i+1t}; \forall i \in I^v, I^v \in V \qquad (6)$$

$$\sum_{I^v \in V} \sum_{i \in I^v} x^v_{it} \le Max; \forall \mathrm{t} \in \mathrm{T} \qquad (7)$$

$$\sum_{t \in T} t.x^v_{I^v t} \le Y; \forall I^v \in V \qquad (8)$$

$$\mathrm{dev}^v_i \ge s^v_i - (\sum_t t.\mathrm{x}^v_{it}); \forall \mathrm{i} \in \mathrm{I}^v, I^v \in V \qquad (9)$$

$$\mathrm{dev}^v_i \ge (\sum_t t.\mathrm{x}^v_{it}) - f^v_i; \forall i \in I^v, I^v \in V \qquad (10)$$

$$dev^v_i \ge 0; \mathrm{x}_{it} \in 0,1; i \in I^v; \mathrm{I}^v \in \mathrm{V}; t \in T \qquad (11)$$

Model has the objective function (2) which is apt to minimize immunization quality loss (immunization effectiveness). Based on the following constraints: constraints group (3) makes sure that each dose of each vaccination series is scheduled at most on one time unit. it's because of preferring the quality of the vaccination to the number of administrated doses. The constraints group (4) ensures that each successor group of doses, can be scheduled, only if their preceding dose is scheduled to be administrated. Constraints group (5) is introduced to recognize the time lag (delay) between each pair of successor doses in vaccine series. It ensures that whenever dose i is administrated in time unit t, then dose i+1 can be scheduled at least D_{it}^{v} time unit(s) after the administration (execution) of dose (activity) i. constraint which is introduced as the (6) makes sure that in each time unit, at most "Max" doses (of any kind) can be administrated. In the constraints group (7), model is forced to schedule (all the vaccine series) before the deadline (Y). At last, Constraints sets (8) and (9) are presented to compute the deviation of x^{v}_{it}s, which are out of the recommended time area (s^{v}_{i} to f^{v}_{i}) time zone.

To state more clearly, in introducing pediatric immunization model, some customizations are explained here. The objective function is inspired, pondering the RCPSPQTS objective function, which is based on minimizing the lost quality of the execution too. It minimizes cost of losing immunization effectivness. As we mentioned before, constraints group (6) is similar to and derived from constraints set in RCPSPQTS and MRCPSP-GPR models, which deals with resource availability. Also, constraints to compute deviations from earliest and latest recommended time units (8 and 9) are devised, pondering constraints for computing Q_i^{loss} in RCPSPQTS model [39]. With some tiny changes, constraints (3) and (5) are derived from constraints about activities time units allocation to only one time slot and constraints about considering the FF^{min} time lags from MRCPSP-GPR model, respectively [48].

Linear model simple example

In this section some computational verifications for the PISP linear model and the project control-based tool will be discussed. The MRCPSP-GPR is strongly NP-hard and finding a feasible solution is NP-complete [50, 68, 69]. Also, the complexity of RCPSPQTS is highly affected by resource constrains and number of time slots as well as the spread of them [51]. The basic RCPSP is considered to be NP-hard [70]. Moreover, cases of immunization scheduling/rescheduling are less likely to be expanded enough to cause computational difficulties (we have tested problems with 20 vaccine series).

Here first we try to solve a simple example of vaccination with the PISP mathematical model using MIP, then based on some changes in cases size and parameters, more analytical investigations will be discussed. We present a case of 8 vaccine series each have 4, 3, 5, 4, 6, 5, 4 and 3 recommended doses to be administrated. Then, we assume that it is just one dose allowed to be administrated in each single time slot (Max=1) and the surcharge for each time slot deviation from the recommended times (BQ) is considered to be 200 and the cost for allocations during the recommended time windows (LQ) is 2. Fanally the big M is 2000. Using CPLEX 12.5.1.0 it just took 1.595 seconds using an Intel™ core i5 CPU to get the solutions. This solution takes about 4 seconds for a problem comprising 20 vaccine series. We ran the model for 5 times on each 36 different combinations of main parameters (number of vaccine series, Max, Y, BQ and LQ). The comparison results from these 180 runs is depicted below in Figure 11 and Figure 12.

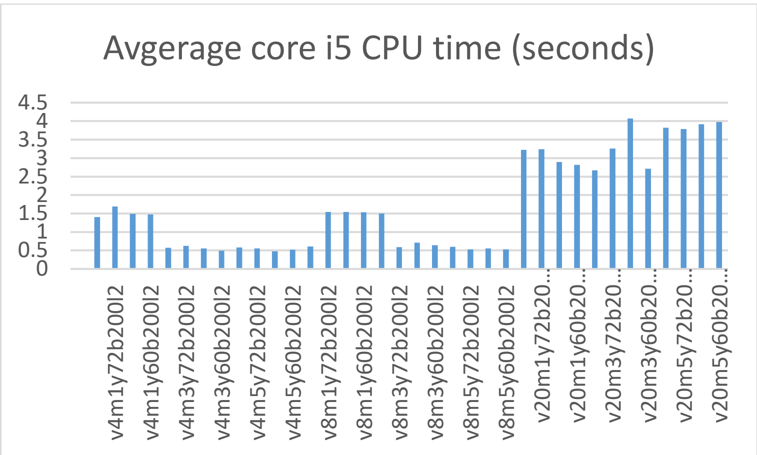

Figure 11. Average CPU time for 36 different combination of main parameters

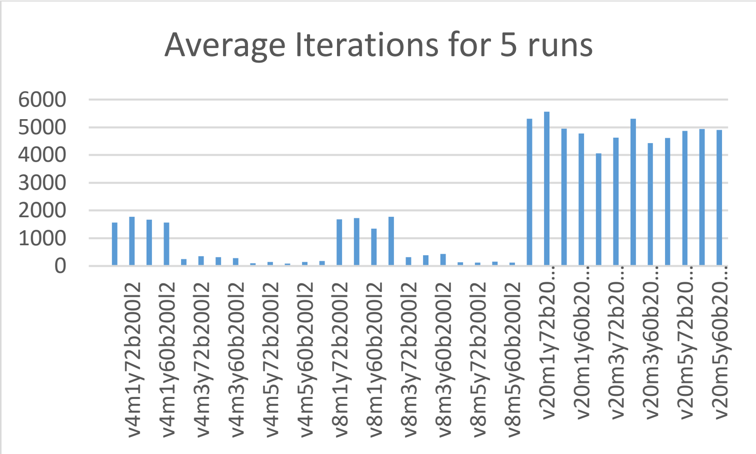

Figure 12. Average number of CPLEX iterations for all 180 PISP runs

As can be resulted from the above figures, PISP complexity, in large part, rides on maximum allowed administrations per time unit (amount of parameter Max). The model itself took no more than 5 seconds to be solved at longest compilation times. Based on such results and considering possible PISP problems enlargements, getting the initial (recommended) plan is not too much time consuming. It is in contrast with what is happening when a catch-up plan is needed. The project-based tool, is devised to deal with catch-up cases. The tool also can be responsible for presenting the baseline (initial) vaccination plan as well.

project control-based tool for catch-up situations (step C)

Dealing with vaccination problem, until now we passed the the two steps of the phase I of the presented framework in Figure 5. Therefore, we have a MPRCPSP-GPR with quality-dependent time slots, which has uncertainty for its activities based on the predecessor tasks execution time. Now we need a useful approach with a good Graphical User Interface (GUI) and computing part (CP). The *GUI part* needs to be user-friendly and comprehensively useful at the same time. Considering so many constraints and considerations in PISP, practitioner needs to have so mnay considerations and exceptions to give a good catch-up plan. This catch-up plan needs to be individualized according to the child's situation. Making decisions based on children's immunization history is the CP's job.

The solution approach is making use of VB programming language in a project-based environment. It is based on project control tools which is totally in harmony with the comprehensive framework idea. In addition, it can provide a very good looking and easy-to-use GUI which can deal with catch-up situations well. Therefore, project-based VBA approach seems to be the best approach. We will discuss this approach and its two parts in the next sections.

The first part, GUI

The project-based approach first part, GUI, needs to be easy-to-use and consist of all the needed facilities at the same time. VB environment is the best choice and project planning sight is the most related basis. It is because in VB environment, we have so many functions and commands, which are written before and are the parts of project control and scheduling procedure and we just have to call them at the best time (in the CP part). This is what is lacking in other VB environments like Microsoft™ Excel. Some tasks like precedence relations adjustments are excessively easier to implement in this VB environment. The *GUI part* mostly is designed using VBA User-forms. Figure 6 and Figure 8 show initial and catch-up plan sections respectively. In Figure 13 a sample of .xlsx format catch-up plan, which is generated by the presented tool is depicted.

ID	Vaccine.DoseNo.	Administrated date	To be Administrated date
1	BCG1	Fri 5/1/15	May 1, 2015 5:00 PM
2	DTP1	Fri 5/1/15	May 1, 2015 5:00 PM
3	DTP2	NA	December 26, 2016 9:29 PM
4	DTP3	NA	May 19, 2016 5:00 PM
5	DTP4	NA	June 12, 2016 5:00 PM
6	DTP5	NA	July 5, 2016 5:00 PM
7	OPV1	Fri 5/1/15	May 1, 2015 5:00 PM
8	OPV2	NA	December 26, 2016 9:29 PM
9	OPV3	NA	May 19, 2016 5:00 PM
10	OPV4	NA	June 12, 2016 5:00 PM
11	OPV5	NA	July 5, 2016 5:00 PM
12	OPV6	NA	July 28, 2016 5:00 PM
13	Hep.B1	Fri 5/1/15	May 1, 2015 5:00 PM
14	Hep.B2	NA	December 26, 2016 9:29 PM
15	Hep.B3	NA	June 12, 2016 5:00 PM
16	MMR1	Fri 5/1/15	May 1, 2015 5:00 PM
17	MMR2	NA	April 26, 2016 5:00 PM

Vaccination_plan

READY

Figure 13. Catch-up plan in an excel readable spreadsheet

The second part, Computation part

This part has better output with project-based approach and needs less coding in VBA environment comparing to other possible ways. The only work we have to do for this part is to call the functions and commands appropriately. For example, in some case, like, when last administrated DTP vaccine series dose is received more than 4 years ago the next dose scheduled for the DTP series is the last dose and all the remaining doses has to be canceled and excluded from the scheduling. This task can be done just by calling the "InactiveToggle" property in project-based VB environment. Figure 8 illustrates the catch-up data entry part of the tool.

Project-based approach additional advantage; EVM (step D)

Not only the project-based (VB) approach gave us a good environment similar to the comprehensive framework idea, but also we can make use of another project control technique, EVM in cost (effectiveness) evaluations. It can be beneficial in some cases. First, it can give a big picture of loses in quality of the immunization in a quantitative shape. Second, having EVM's indices in mind, it can provide a good basis for further researches on immunization cost evaluations. In the project-based tool, the EVM report is available only when there is a call for a catch-up plan (see Figure 14). The tool is devised to save a baseline for the immunization plan using the child's birthday. Then, as the last visit date will be the status date for the vaccination project, VB environment initiates the earned value report.

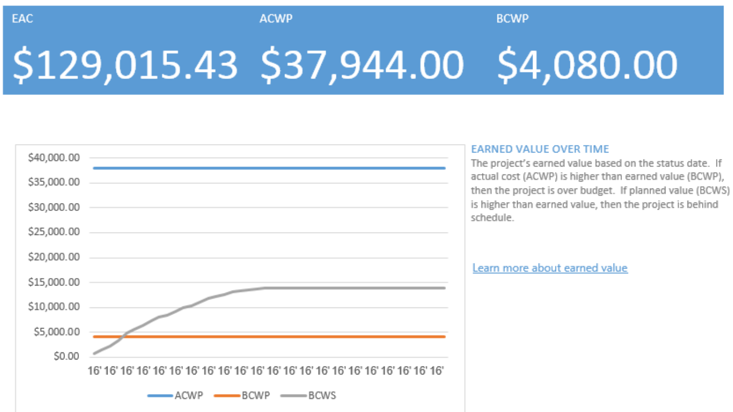

Figure 14. Earned value report for the presented catch-up plan

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