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Vaccine wastage reduction in immunization sessions through vaccine vial size optimization

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by

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Dedication

This thesis is dedicated to my grandparents and my parents for their moral support, patience and trust in me.

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Abstract

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Outreach sessions are immunization services in which health workers immunize children in their communities, are needed to improve vaccine coverage in rural areas of developing countries. These services face very high open vial wastage, which happens when vaccine doses stored in a vial are not used within a specified time after the vial is opened. Such open vial wastage is directly caused by the choice of vial size used and the session size (number of pariticipants attending an outreach session) for which the outreach sessions are planned. The open vial wastage decreases with increase in session size. However, controlling the session size is not practical. Hence, this thesis proposes reducing open vial wastage through the choice of vial size. The choice of a single dose vial reduces the likelihood of open vial vaccine wastage; but it increases the vaccine purchase cost per dose compared to that of larger vial sizes. This study proposes two methodologies, based on stochastic optimization and binary integer programming models. Both methods compute the optimal vial size and the reorder point to be used by a vaccine store that plans for immunization sessions in a developing country, while dealing with the tradeoff between vaccine purchase cost and the open vial wastage, as a function of vial size. The proposed methodologies are used to recommend the optimal vial size to be used in

Bangladesh for Bacille Calmette-Guerin (BCG) vaccine and Measles vaccine. Additionally this thesis applies the proposed methodologies to study the effect of session size and vaccine vial size on the open vial wastage. Finally this thesis suggests how knowing the optimal vial size can result in financial incentives that could be offered to participants of immunization sessions to increase participation of people in immunization sessions.

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Chapter 1

Introduction

Vaccines are perishable products distributed in vials. Once a vaccine vial is opened, all the doses stored in the vial have to be used within a given length of time referred as open vial lifetime (OVL). In case of an open vial, once its OVL has elapsed, any unused vaccine doses left in the vial are wasted. Such a wastage is referred as open vial wastage (OVW). The OVL is different from the expiration date of the vaccine vials, which depends on the shelf-life of the unopened vaccine vials. The OVW is just one of the many forms of vaccine wastage incurred during immunization activities. In a vaccine wastage study conducted in Bangladesh [8] in 2004, the percentage of vaccines procured for immunization that were wasted from vials that were opened, including OVW, was 85% for Bacille Calmette-Guerin (BCG) vaccine, 71% for Measles vaccine, 44.2% for Diphtheria, Pertussis and Tetanus (DTP) vaccine and 36.6% of Tetanus Toxoid (TT) vaccine. In a vaccine wastage assessment study conducted in India [17] between 2009 and 2010, the average vaccine wastage, including OVW, was 61% for BCG vaccine, 35% for Measles vaccine, 27% for DTP vaccine, 34% for TT vaccine and 47% for Oral Polio vaccine (OPV). In order to deal with such large vaccine wastage, immunization planners in developing countries must order in excess to account for the expected wastage, which strains the existing limited vaccine supply [18], and makes immunization services more expensive. In developing countries like India and Bangladesh, immunization activities among the rural areas of the country are organized by

government agencies or non-profit organizations such as United Nations Children's Fund (UNICEF). Given the limited budgets of such government agencies and organizations, increase in cost of immunization services due to excessive wastage severely limits the expansion of immunization efforts in rural areas. Therefore, reducing OVW can not only reduce costs, but further extend global immunization efforts. OVW during immunization sessions can be attributed to small session size and use of large vial size. In order to reduce the OVW among developing countries, it is necessary to understand the vaccine distribution systems among those countries. The following description of a vaccine distribution system in Bangladesh [8] will be used in this study to generalize the vaccine distribution systems among other developing countries.

In Bangladesh [8], the vaccine distribution system is made up of three echelons. The first echelon consists of a central vaccine store which distributes vaccine vials to district level vaccine stores in the second echelon of the distribution system. These district level vaccine stores further distribute vaccine vials to much smaller vaccine stores called upazila vaccine stores (UVS), in third echelon of the supply chain. At UVS, vaccine doses are used to immunize people through two different types of immunization sessions. In the first immunization session type, the UVS immunizes walk-in individuals from the community, and it is referred as drop-in center sessions. In the second type of immunization session, referred as outreach sessions, health workers take vaccine vials to a specific rural area where people will be immunized at temporary gatherings. Drop-in center sessions are held throughout the year while outreach sessions for a specific rural area are held periodically as determined by each UVS. In Bangladesh [8], drop-in center sessions account for 6% of immunization while outreach sessions account for 94% of immunization. In this study, we consider a vaccine distribution store (VDS) in a developing country that corresponds to the UVS at the third echelon of the vaccine distribution system of Bangladesh and

plans for both types of immunization sessions in a district. The VDS also acts as the last point of vaccine storage in the vaccine distribution system and orders for vaccine vials based on a lot sizing policy. We propose that each VDS is allowed to use a different vial size for each type of vaccine distributed by it and places orders of vaccine vials to vaccine stores in higher echelons of the vaccine distribution system of the country. The OVW during immunization sessions conducted by a VDS, is highly affected by their choice of vaccine vial size (i.e., number of doses stored in the vial) and the session size (i.e., the number of people for which the immunization sessions are planned in a day).

To reduce the OVW in immunization sessions, VDS planners can have larger session sizes or decide to use smaller vial sizes [17]. Inducing larger session sizes for immunization sessions in rural areas of developing countries is difficult and impractical because attendance to these sessions depend on multiple factors such as familiarity of people with immunization, accessibility to venues used for outreach sessions, volunteer availability, poorly motivated health workers and local political support [2, 12]. These factors are out of control for VDS planners. However, the VDS planners can control the choice of vaccine vial size used in their planned immunization sessions. Furthermore, choosing the best vaccine vial size is a complex task. Using a single dose vial for immunization sessions results in no OVW, but incurs higher purchase cost (defined as the total cost incurred until the arrival of an order of vaccine vials to VDS) per dose compared with those for multi-dose vials. However, choosing multi-dose vials results in higher OVW. Therefore, the VDS planners must deal with a tradeoff between the purchase cost per dose and the OVW as a function of the vial size. This study addresses the problem of determining the vial size and the reorder point to be used by a VDS that minimizes the sum of vaccine purchase cost, vaccine vial inventory holding cost and wastage cost due to OVW incurred by a VDS during a planning horizon. The two methods presented in

this thesis solve for the vial size and reorder point that will reduce the total cost (i.e., purchase, holding and wastage due to OVW) at the VDS under stochastic demand for a given vaccine. We assume the planning horizon of VDS to be long enough to make multiple orders based on a reorder policy. The first method computes minimal expected cost per session for VDS during planning horizon for various options of vial sizes available in the market based on a stochastic optimization model. The second method is a Monte Carlo simulation model with binary integer program (BIP) in which random instances of demand are solved to compute minimal cost per session for a VDS during a planning horizon for various options of vial sizes available in the market. In both methods the vial size with least cost per session for VDS is recommended as the optimal vial size.

Chapter 2

Literature Review

The VDS considered in this study is assumed to plan for immunization sessions throughout the year. Hence, the VDS implements a lot sizing policy to be able to meet vaccine demand and maintain an inventory of vaccine vials. Lot sizing studies that have been studied relating to VDS can be broadly classified into four types: [a] studies on lot sizing of products with expiration date; [b] studies on lot sizing of products with OVL; [c] studies on fixed batch size reorder policies as VDS orders vaccine vials of fixed vial size for a given vaccine and [d] studies that recommend guidelines to choose vaccine vial size.

2.1 Studies on lot sizing of perishable products with expiration date

Lot sizing of perishable products under stochastic demand has been the focus of study of several researchers and practitioners. Van Zyl [21], Weiss [23], Cohen [4], Nahmias [14], Nahmias and Wang [16], Lian and Liu [11] among others consider the effect of expiration of perishable products on their reordering policy. Van Zyl [21] shows that the optimal reordering policy for perishable products with single period lifetime under stochastic demand is a continuous review policy that orders only if the inventory level drops below a reorder point s and orders up to a quantity S. Weiss [23]

shows that a continuous review (*s,S*) policy is optimal for perishable products with constant shelf life. Cohen [4] suggests conditions for determining the optimal (*s,S*) policy for perishable products that expire in two time periods under stochastic demand conditions, but fails to suggest conditions for products that perish beyond two time periods. Nahmias [14] concludes that it is not possible to determine the optimal reordering policy for perishable products with lifetimes that extend beyond two periods. For such perishable products with exponential decay, Nahmias and Wang [16] propose a heuristic approximation to determine the lot size Q, and the reorder point r, under Poisson demand and constant lead time. Lian and Liu [11] analyze a discrete time (*s,S*) continuous review policy with instantaneous replenishment and develop a closed form expected cost function for perishable products with geometrically distributed batch demand. For a detailed review of inventory theory on the expiration of perishable products see [15]. Section 2.2 describes studies that have dealt with wastage of similar nature to the OVW occurring in open vaccine vials. Note that vaccines also perish due to expiration date. In this study the only form of vaccine wastage considered for a VDS is the OVW.

2.2 Studies on products with OVL

For a perishable inventory system governed by continuous review (*S,s*) policy, Ravichandran [19] proposes a complex though intractable stochastic analysis to determine the optimal parameters of the (*S,s*) policy. The (*S,s*) policy places orders of a fixed size (*S*-*s*) when the inventory position reaches a reorder level *s* [19]. Ravichandran's analysis assumes product demand to follow Poisson distribution, random replenishment lead time and known fixed lifetime of a product batch since its arrival [19]. Ravichandran also assumes a special aging process (a fresh batch arriving in inventory does not start aging until all units of the previously open batch are exhausted by

demand or decay) that renders his stochastic analysis tractable [19]. Tekin et al. [20] propose a continuous review lot sizing reorder (Q,κ,ρ) policy for products that start aging after all units of a previously open batch are completely used or perish due to decay. The (Q,κ,ρ) policy places an order of constant size Q every time when the inventory drops to κ units, or when ρ time units have elapsed since the last time an order of Q products was received, whichever occurs first [20]. Tekin et al. [20] assume Poisson demand, constant lead time and known fixed lifetime of products in an open batch and propose a fixed order quantity lot sizing policy for perishable products with aging process similar to vaccines. There is no work found in the literature that considers a fixed batch size lot sizing policy for vaccines. Lee et al. [10] is the only work found in the literature that addresses the wastage of vaccine doses in open vials that expire. Lee et al. [10] propose an agent based simulation model to study the expired doses assuming Poisson demand for clinics that conduct immunization sessions and compute optimal vial size to be used for arrival rates to the clinic ranging from 1 to 50 per day for pediatric vaccines such as Measles, BCG, Haemophilus influenzae type b (Hib) vaccine and Pentavalent vaccine (Diphtheria-Tetanus-Pertussis-Hepatitis B-Haemophilus influenzae type b (DTP-Hib-HepB)). Lee et al. [10] do not consider its effect on the vaccine vial reorder policy and hence the problem dealt with by Lee et al [10] is different from the problem statement of this thesis. The optimal vial sizes computed by Lee et al. [10] are compared with the results of the methods proposed in this thesis. Thus there is no study in the literature that addresses the problem considered in this thesis.

2.3 Studies on fixed batch size reorder policies

Veinott [22] implements (k,Q) policy for a dynamic inventory problem for non-perishable products with independent and identically distributed random demand, constant lead time, discount factor and no cost for placing an order and proves the optimality of (k,Q) policy. The (k,Q) policy is a continuous review policy in which, an order is placed in multiples of Q if the inventory position is less than k [22]. The order size is the smallest multiple of Q that will bring the inventory position after order placement to at least k [22]. Hadley and Whitin [9] consider a discrete review (nQ,r,T) policy for a non-perishable inventory system, that reviews inventory level only at fixed intervals of time T and determines the size of the order similar to that of Veinott's (k,Q) policy [22]. Hadley and Whitin [9] also derive an exact cost function for their batch ordering (nQ,r,T) policy when there is a Poisson demand, constant lead time and backorders. Such a cost function is then minimized with a service level constraint [9]. The reason for choosing (nQ,r,T) policy [9] over (k,Q) policy [22] for a VDS is explained in Chapter 3.

2.4 Current guidelines for selecting vaccine vial size

The Global Alliance for Vaccine Immunization (GAVI) propose a guideline to decide upon the vial size for the immunization sessions [7]. GAVI's guideline uses the wastage rate for single dose vial as an input and then it performs a local search to determine the wastage rate at which the total cost for each of the other vaccine vial sizes considered breaks even with the total cost for a single dose vial. The total cost for a vial includes the purchase, the storage and the transportation costs incurred in bringing a vial to the destination. However, this model does not provide further guidelines to choose the optimal vial size based on the breakeven wastage rates computed for different vial sizes. Furthermore, the GAVI model does not consider the

stochastic nature of demand. In India, UNICEF and National Rural Health Mission, India [17] conducted a vaccine wastage assessment study in 2009-2010 based on observations from vaccine stores in five selected states [17]. For different vial sizes, projected wastage rate was computed based on the observed wastage rate for currently used vial size. Analysis on the optimal vial size was carried out by comparing the projected wastage rate and the storage volume per dose between different vial sizes for Bacille Calmette-Guerin (BCG), DPT, Measles, HepB, Tetanus Toxoid (TT) and Oral Polio (OPV) vaccines [17]. The projected wastage rate computed in [17] does not consider the stochastic nature of the demand faced by the vaccine stores and its effect on the OVW in immunization sessions. There are no current guidelines for choosing vial size that deal with stochastic demand.

Chapter 3

Methodology

This study proposes two methods to compute optimal vial size and reorder point for a VDS. The first method is based on a stochastic optimization model further referred as SOM method, and the second method is based on a Monte Carlo simulation model that consists of a binary integer programming (BIP) model, further referred as BIP method. The SOM method is restricted to Poisson demand while the BIP method can handle any demand distribution for VDS. Apart from OVW during immunization sessions, the BIP method also accounts for unused doses from open vials at the end of an immunization session as OVW, which is the case with immunization sessions. The SOM method accounts only for OVW during immunization sessions. Thus BIP method represents immunization sessions better than SOM method. However, BIP method needs expensive computing resources compared to SOM method as explained in Section 4.1.

3.1 Common assumptions for SOM method and BIP method

Both methods can be used by VDS administrators to plan for immunization sessions during a planning horizon. Both methods assume that in a given immunization session, vaccine vial is opened only after a previously opened vial is completely used or its OVL has elapsed which is usually the

case with immunization sessions. Additionally the models assume that a participant vaccinated by the VDS requires only one dose. However for vaccines that require multiple doses for complete immunization of an individual, optimal vial size computed by both methods have to be multiplied with number of doses required for complete immunization of an individual. The lead time for receiving an order of vaccine vials by the VDS is assumed to be known and constant. This is a justified assumption as orders for a VDS is assumed to arrive from vaccine stores within the same country. The VDS expects to have a 100% service level as the objective of immunization sessions is to improve vaccine coverage among developing countries. When planning for immunization sessions, the model assumes that the session size distribution during the planning horizon is known and that each VDS conducts only one immunization session per day, which is not usually the case. But both methods can be easily extended to a VDS that plans for multiple immunization sessions per day as explained in Appendix I. Furthermore, it is assumed that the OVW is the only significant form of vaccine wastage at the VDSs. Other forms of wastage such as reaching of expiration date of the vaccine vial, exposure of vaccine vial to improper temperature, breakage of vaccine vials, suspected contamination of opened and closed vaccine vials, poor vaccine reconstitution and administration practices and not being able to draw the number of doses indicated in the label of a vial are not considered. This assumption restricts both methods from capturing all forms of vaccine wastage during immunization sessions. For a given vaccine, VDS is assumed to order only one vial size during the planning horizon. Hence a fixed batch size reorder policy that orders vaccine vials of constant vial size suits a VDS. A continuous review policy is not advisable for a VDS, because it is not feasible to continuously monitor inventory levels during the immunization activities in rural areas and at VDS. Hence a periodic review batch ordering, (nQ,r,T) policy, proposed by Hadley and Whitin [9] is chosen as the reordering policy for a VDS and the policy is explained as follows. If the vial inventory position during review

y, is less than or equal to reorder point *r*, an order of *n* vials of containing *Q* doses is placed, which arrives after lead time *L* [9]. The number of vials to be ordered, *n*, is chosen such that $r < y+nQ \leq r+Q$ [9]. Section 3.2 describes the SOM method and Section 3.3 describes the BIP method.

3.2 SOM method

A flowchart shown in Figure 3.1 describes the steps involved in SOM method. For all the vial sizes considered, SOM method minimizes reorder point to be followed by a VDS, guaranteeing a service level and the expression for expected cost per session for VDS is evaluated. The vial size with minimal expected cost per session is recommended as optimal vial size to be used by VDS. In addition to assumptions described above, the SOM method assumes demand to follow Poisson distribution and allows backorder of vaccine doses, as 100% service level cannot be guaranteed by this method. The expression for expected OVW per session is derived based on framework proposed by Tekin et al. [20], as explained in the subsection 3.2.1. The stochastic optimization model that computes optimal reorder point and the expressions to compute expected cost per session are explained in the subsection 3.2.2.

3.2.1 Expression for expected OVW per session

Similar to work presented by Tekin et al. [20], let X_n be the random variable representing arrival time of n^{th} person with distribution function $F_n(t)$ and let $N(t)$ be the counting process associated with Poisson demand process in $(0,t]$. Let λ be the expected arrival rate per session for a VDS (same as average session size for a VDS) during the planning horizon. The expected OVW per session is then calculated as the ratio of expected OVW per cycle (referred as *E[OVW]*) to the expected cycle length (*E[CL]*) in number of

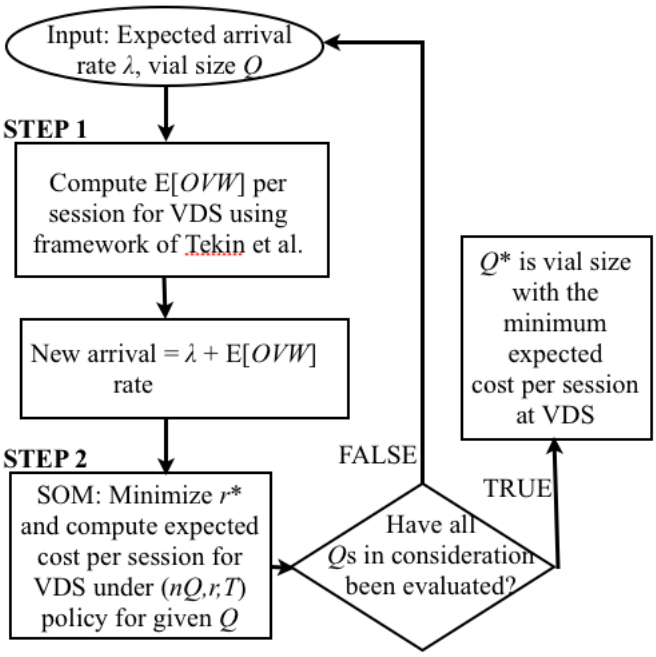

Figure 3.1: Flowchart describing steps involved in the proposed SOM method

sessions. The cycle length is defined as the time between successive opening of vaccine vials. One can compute two different values for cycle length and OVW in a cycle depending on the arrival time of Q^{th} person. The first set of values happens when, in a cycle, the Q^{th} person arrives before the OVL elapses as shown in Figure 3.2. The cycle length takes the value of the arrival time of the $(Q+1)^{th}$ person, as a new vaccine vial will be opened only when the $(Q+1)^{th}$ person arrives. The OVW in that cycle is zero as all the Q doses were utilized by the Q demands. The second set of values happens when, in a cycle, the Q^{th} person arrives after the OVL (OVL= τ) has elapsed as shown in Figure 3.3. Then, the cycle length takes the value of the sum of τ and the inter-arrival time, by virtue of the memoryless property of exponential distribution. The OVW in that cycle corresponds to $(Q\text{-}N(\tau))$, as only $N(\tau)$ doses are used. The equations (3.1) and (3.3) describe the expressions for the expected cycle length and the expected OVW. Equations

(3.2) and (3.4) present the final expressions for expected cycle length per unit time and expected OVW per cycle. For a given Q, the expected OVW per session ($\Omega(Q, \lambda, \tau)$) and the expected wastage cost per session due to OVW are given by equations (3.5) and (3.6) respectively.

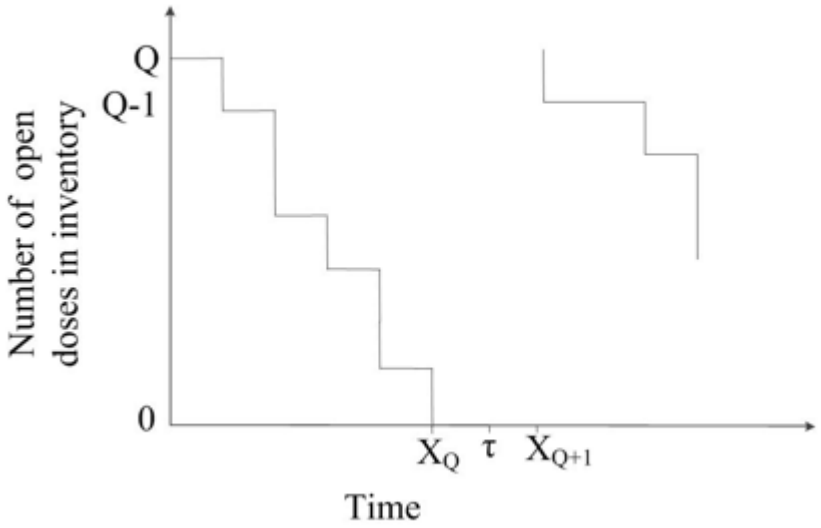

Figure 3.2: Scenario 1: Zero OVW

$$E[CL] = E[(X_{Q+1})I(X_Q \leq \tau)] + E[(\tau + \frac{1}{\lambda})I(\tau < X_Q)] \tag{3.1}$$

$$E[CL] = (\frac{Q+1}{\lambda})F_Q(\tau) + (\tau + \frac{1}{\lambda}) * (1 - F_Q(\tau)) \tag{3.2}$$

$$E[OVW] = E[(Q - N(\tau))I(\tau < X_Q)] \tag{3.3}$$

$$E[OVW] = Q(1 - F_Q(\tau)) - \lambda\tau(1 - F_{Q-1}(\tau)) \tag{3.4}$$

$$\textit{Expected OVW per session } \Omega(Q, \lambda, \tau) = \frac{E[OVW]}{E[CL]} \tag{3.5}$$

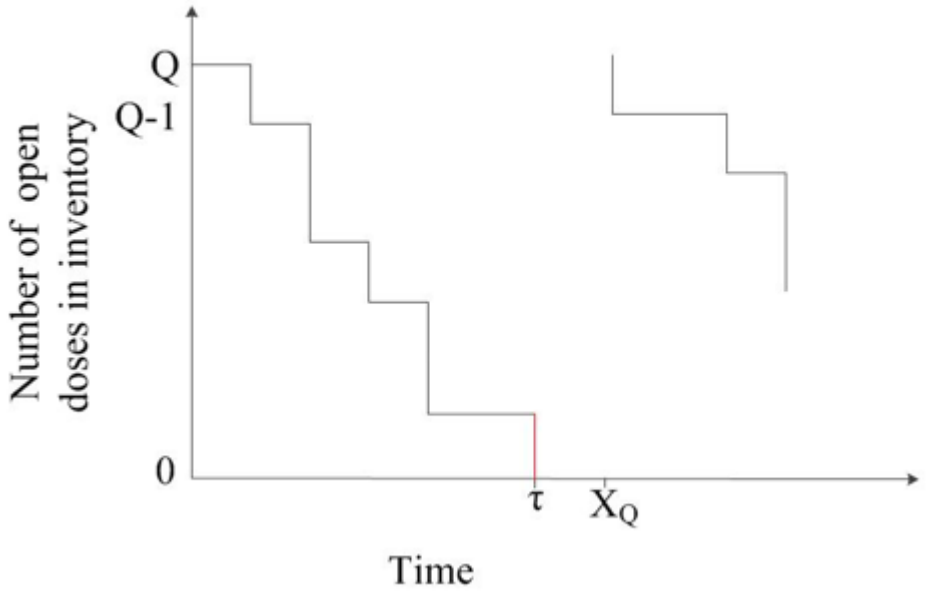

Figure 3.3: Scenario 2: Non zero OVW

$$\textit{Expected wastage cost per session due to OVW} = \varsigma\Omega(Q, \lambda, \tau) \quad (3.6)$$

where:
τ : OVL of the vaccine
I() : indicator function that takes a value 1 if the argument is true and 0 if the argument is false
In an immunization session, OVW occurs during the session and also at the end of the session. The number of unused doses at the end of an immunization session is considered as wastage. Thus the SOM method only captures OVW that occurs during the session. The following subsection describes the resulting stochastic optimization model used to compute the optimal reorder point for a given vial size Q and an arrival rate.

3.2.2 Stochastic optimization model

This study proposes the VDS to follow (*nQ,r,T*) policy [9], as explained in Section 3.1. Hadley and Within [9] present a stochastic optimization model that minimizes total cost per unit time incurred by a non-perishable

inventory system. In this study, we modify the Hadley and Within's [9] stochastic optimization model by incorporating the expected OVW per session (equation (3.5)), and adding a service level constraint (equation (3.8)). Such constraint limits the value of the expected number of backorders per unit time, incurred by VDS, to α. Since VDS is assumed to have very high service level, the cost incurred by VDS due to backorder is negligible. The resulting optimization problem minimizes reorder point subject to a service level constraint as described below.

Variables
r : reorder point (doses)

Parameters
$\lambda+\Omega(Q,\lambda,\tau)$: average session size for VDS during planning horizon after accounting for OVW (participants/session)
τ : OVL of the vaccine
Q : vaccine vial size (doses/vial)
L : lead time associated with arrival of vaccine orders placed by VDS (days)
T : fixed length of time between successive reviews on inventory level, called review period (days)
C : vaccine purchase cost per dose ($/dose)
I : vaccine inventory holding cost per dose, percentage of purchase cost (%)
ς : wastage cost per dose due to OVW ($/dose)
(1-α): service level, defined as the fraction of satisfied demand (%)

Functions:
p_r(nQ) : probability that *n* vials of size *Q* will be ordered after a review
$K'_T(Q)$: average vaccine purchase cost per session ($/session)

$E'(Q, r, T)$: expected number of vaccine backorders per session ($/session)

$$\textbf{Minimize: } r \tag{3.7}$$

$$\textbf{subject to: } E'[Q, r, T] \leq \alpha \tag{3.8}$$

$$r \geq 0 \tag{3.9}$$

Also note that, average vaccine inventory holding cost per session

$$= IC(\frac{(Q+1)}{2} + r - \frac{(\lambda + \Omega(Q, \lambda, \tau))T}{2} - (\lambda + \Omega(Q, \lambda, \tau))L + E'(Q, r, T)) \tag{3.10}$$

$$K'_T(Q) = \frac{1}{T} \sum_{n=1}^{\infty} CnQp_r(nQ) \tag{3.11}$$

The resulting *r* for a given *Q*, obtained from the solution of the above minimization problem is then used to evaluate average inventory carrying cost per session from equation (3.10) and average purchase cost per session from equation (3.11). The expression for function $E'(Q, r, T)$ can be obtained from Hadley and Whitin [9] by replacing λ with $(\lambda + \Omega(Q, \lambda, \tau))$. For a given *Q*, the expected cost per session incurred by VDS is computed as the sum of expected purchase cost per session, expected wastage cost per session due to OVW and vaccine inventory holding cost per session. The expected cost per session incurred by VDS is then computed for different values of *Q*. The optimal vial size *Q** is the one with the minimum expected cost per session and the reorder point *r* corresponding to *Q** is the optimal reorder point recommended for VDS.

3.3 BIP method

A flowchart shown in Figure 3.4 describes the steps involved in binary integer program method. The BIP method is a Monte Carlo simulation model that consists of two steps. The BIP method discretizes the planning horizon of a VDS into fixed number of periods. The first step of the BIP method is called the demand generator algorithm and the second step is a BIP optimization model. For each vial size considered, the demand generator algorithm has the demand distribution, the mean of the demand distribution and the length of a period as its inputs. The demand generator algorithm generates random instances of demand and computes the number of vials to be opened, and the OVW incurred in every period of the planning horizon of a VDS. For each vial size considered, the BIP uses as input, the computed OVW and the number of vials opened for each period of the planning horizon from the demand generator algorithm to solve a BIP for a given demand instance. The BIP minimizes the sum of vaccine purchase cost, inventory holding costs and the opportunity cost due to OVW at the VDS, during the entire planning horizon. The BIP considers the reorder point as the decision variable. Since instances of demand are randomly generated to obtain the optimal solutions, the two steps have to be replicated to obtain a robust estimate on solutions from the BIP with a required confidence level. The number of replications K, is calculated based on the methodology proposed by Centeno and Reyes [3] for simulating terminating systems. For each replication, the solution from BIP consists of optimal cost and the optimal reorder point for the VDS. The average of optimal cost obtained from K replications is obtained as the average cost for VDS. The vial size with the minimum average cost is recommended as the optimal vial size and the average reorder point associated with that vial size is the recommended reorder point.

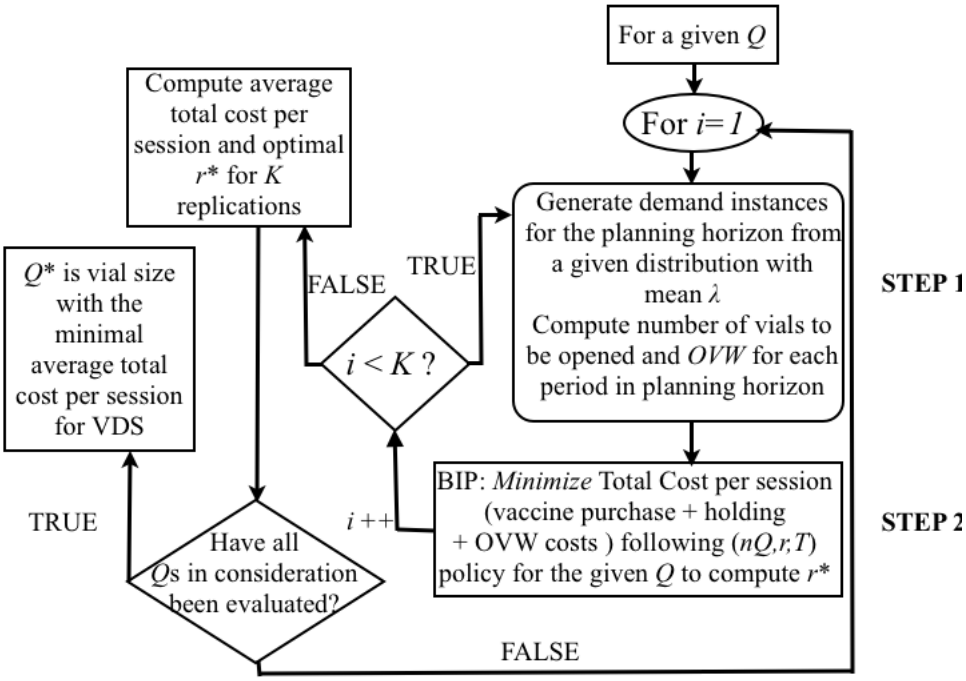

Figure 3.4: Flowchart describing steps involved in the proposed BIP method

A complete description for the demand generator for a Poisson demand distribution is given in Appendix B. With input such as demand, number of vials opened and OVW for every period of the planning horizon from the demand generator, the BIP is solved, with reorder point for VDS as the decision variable. The objective of the BIP is to minimize the sum of the purchase, inventory holding and OVW costs following a (nQ,r,T) reorder policy proposed by Hadley and Whitin [9]. When solving the BIP, the initial inventory available in the VDS is considered a variable because assigning a fixed value to the initial inventory restricts the values taken by the decision variable reorder point. To prevent the BIP from starting with a very large inventory of vaccine vials and to make reorder of vaccine vials necessary to meet demand of VDS during the planning horizon, the purchase cost of initial inventory is included in the objective of the BIP. The BIP is explained as follows.

Parameters:
B: number of working minutes in a day (minutes)
b: length of a period (minutes)
P: planning horizon in periods, $\frac{\text{UB}}{\text{b}}$
d_i: demand in i^{th} period (doses)
N_i: number of vials opened at the beginning of i^{th} period (vials)
W_i: OVW at the end of i^{th} period (doses)
C: purchase cost per dose for a given vial size ($/dose)
E: inventory carrying cost per day per dose for a given vial size ($/dose)
ς: wastage cost per dose, constant, ($/dose)
T: review period (number of periods), $\frac{\text{review period in days B}}{\text{b}}$
L: lead time (number of periods), $\frac{\text{lead time in days B}}{\text{b}}$
g: Floor $[\frac{L}{T}]$, constant, number of review periods taken by an order to arrive
h: Floor $[\frac{P}{T}]$, constant, number of times inventory is reviewed during the planning horizon
M: large positive constant

Variables:
I_i: number of doses in opened vial available at the beginning of period i, $I_i \geq 0$
o_i: 1 if an order is placed in a period i; 0 otherwise
r: reorder point for the (*nQ,r,T*) periodic review policy, r ≥ 0
V_i: number of vaccine vials ordered in a given review period i, $V_i \geq 0$

BIP

$$\textbf{Minimize: } \sum_{i=1}^{P}[V_i\ Q\ C + W_i\ \varsigma] + \sum_{k=1:k\ mod\ \frac{B}{b}=0}^{P} [I_k\ E] + I_1 C \quad (3.12)$$

subject to:

$$I_{i.T} \geq r - M\ o_{i.T} \qquad \forall\ i\ \in\ 1....\lfloor\frac{L}{T}\rfloor \tag{3.13}$$

$$I_{i.T} \leq r + 1 + M\ (1 - o_{i.T}) \qquad \forall\ i\ \in\ 1....\lfloor\frac{L}{T}\rfloor \tag{3.14}$$

$$I_{i.T} + \sum_{j=1}^{g} V_{(i-j).T}\ Q \geq r - M\ o_{i.T} \qquad \forall\ i\ \in\ (\lfloor\frac{L}{T}\rfloor + 1)....\lfloor\frac{P}{T}\rfloor \tag{3.15}$$

$$I_{i.T} + \sum_{j=1}^{g} V_{(i-j).T}\ Q \leq r + 1 + M\ (1 - o_{i.T}) \qquad \forall\ i\ \in\ (\lfloor\frac{L}{T}\rfloor + 1)....\lfloor\frac{P}{T}\rfloor \tag{3.16}$$

$$o_1 = 0 \qquad \forall\ i\ in\ 1....P:\ i\ mod\ T\ \geq\ 1 \tag{3.17}$$

$$V_i \leq M\ o_i \qquad \forall\ i\ in\ 1....P \tag{3.18}$$

$$I_{i.T} + V_{i.T}\ Q \leq r + Q \qquad \forall\ i\ \in\ 1....\lfloor\frac{L}{T}\rfloor \tag{3.19}$$

$$I_{i.T} + V_{i.T}\ Q \geq r + 1 \qquad \forall\ i\ \in\ 1....\lfloor\frac{L}{T}\rfloor \tag{3.20}$$

$$I_{i.T} + V_{i.T}\ Q + \sum_{j=1}^{g} V_{(i-j).T}\ Q \leq r + Q \qquad \forall\ i\ \in\ (\lfloor\frac{L}{T}\rfloor + 1)....\lfloor\frac{P}{T}\rfloor \tag{3.21}$$

$$I_{i.T} + V_{i.T}\ Q + \sum_{j=1}^{g} V_{(i-j).T}\ Q \geq r + 1 \qquad \forall\ i\ \in\ (\lfloor\frac{L}{T}\rfloor + 1)....\lfloor\frac{P}{T}\rfloor \tag{3.22}$$

$$\mathrm{N_i}\ \mathrm{Q} \leq \mathrm{I_i} \qquad \forall\ \mathrm{i}\ \in\ 1....\mathrm{P} \tag{3.23}$$

$$I_{i+1} = I_i - d_i - W_i \qquad \forall\ i\ \in\ 1....(L + T - 1) \tag{3.24}$$

$$I_{i+1} = I_i - d_i - W_i + V_{i+1-L}\ Q \qquad \forall\ i\ \in\ (L + T)....(P - 1) \tag{3.25}$$

$$I_i,\ V_i\ \geq\ 0; \qquad o_i\ \in\ \{0,1\} \tag{3.26}$$

The objective function (3.12) minimizes the sum of purchase, holding and OVW costs and the purchase cost of the initial inventory. Constraints (3.13) to (3.22) limit order placements in a given review period based on (*nQ,r,T*) policy. Constraint (3.23) ensures there is no shortage of vaccine vials during any period. Constraint (3.24) and (3.25) keep track of inventory of vaccine doses in the system and constraint (3.26) is the non-negativity constraint. The accuracy of the optimal cost and the optimal reorder point obtained from the BIP and the time taken to solve the BIP depend on the value assigned to the length of a period (*b*) parameter. Assigning large values for parameter *b* (e.g., 1day, 5 days) would result in less accurate solution compared to smaller values of *b*. However, for smaller values of *b*, the number of non binary and non integer variables in BIP increase resulting in longer time taken to solve the BIP.

Chapter 4

Experimental Results

In order to demonstrate the application of the two methods developed in this study, six experiments are presented in this thesis. In the first experiment, we observe the effect of session size on optimal vial size using both proposed methods. The results from a similar experiment performed by Lee et al. [10] is compared with the results from both the methods. In the second experiment, we study the behavior of expected OVW per session as the vial size is increased for a given session size and as the session size is increased for a given vial size using BIP method. In the third experiment, we study the effect of session size on optimal cost per participant incurred by VDS using SOM method. In the fourth experiment, we study the effect of the vaccine purchase cost on the optimal vial size using SOM method. In the fifth experiment, we recommend vial sizes for BCG and Measles vaccine for Bangladesh based on data for session size from the literature using BIP method. In the sixth experiment we study the tradeoff between accuracy of average cost computed using BIP method and the time taken to solve the BIP. The experimental conditions for all the six experiments have been listed in Table 4.1. All the values in the table are chosen for the purpose of experimentation and may relate to real world instances. The purchase cost per dose for vaccines considered in the experiments are obtained from Lee et al. [10] as listed in Table 4.2. In all the experiments, the BIP method is replicated 500 times for a planning horizon of 120 days and each day has 8 hours of immunization activities. Also the length of a period is 5 minutes

for BIP method, except for the final experiment.

Table 4.1: Experimental parameters

Parameters	Values
OVL for all vaccines	6 hours
Session length	8 hours per day
Lead time	5 days
Review period	7 days
Inventory holding cost per day per vial	10% of Purchase Cost per vial
Wastage cost per dose	same as Purchase cost per dose
Service level	100% for BIP method, 99.9% for SOM method

Table 4.2: Vaccine vial sizes considered for experiment and their purchase cost

Vaccine	Vial sizes in consideration	Corresponding purchase cost per dose [10]
Measles	1, 5, 10	\$0.943, \$0.633, \$0.246
Hib	1, 2, 10	\$3.619, \$3.42, \$1.83
BCG	10, 20	\$0.191, \$0.104
Pentavalent	1, 2, 10	\$3.6, \$3.5, \$2.0

4.1 Effect of session size on Q^*

The two methods proposed in this study are validated by comparing the generated results with those reported by Lee et al. [10] for an incoming Poisson demand. Figure (4.1) shows the optimal vial sizes for various session sizes for the vaccines mentioned above. In case of Measles vaccine, all three models indicate that 5 dose vial size is not optimal for any session size and the results from all three models are consistent. In the case of Hib and DTP-Hib-HepB (Pentavalent) vaccines, results from the BIP method and Lee et al. [10] model are consistent and do not recommend 2 dose vial

while the SOM method recommends 2 dose vial for session sizes 5 to 7 for Hib vaccine and session sizes 6 to 8 for DTP-Hib-HepB vaccine. In the case of BCG vaccine, results from both the proposed methods show that 10 dose vial size is optimal until session size 14 and 20 respectively, while the Lee et al. [10] model suggests 10 dose vial to be optimal until session size 6. The difference in the results can be explained as follows. Lee et al [10] compute number of unused doses at the end of session as OVW and does not account for OVW during a session. SOM method computes expected OVW during session and do not account for OVW at the end of a session. BIP method accounts for OVW during the sessions and at the end of the session. The difference in the computation of OVW in each of the model results in different results. As the results of three models are similar despite this difference, we conclude the two methods are validated. BIP method captures OVW closest to what happens in reality. On an average, the SOM method takes 10 hours to compute average cost per session for vial sizes from 1 to 20, for a given session size using a 3 GHz, 1 GB RAM computer and is solved using Mathematica software. On an average, the BIP method takes 6 hours to compute average cost per session from 500 replications of BIP method, for vial sizes from 1 to 20, for a given session size using four computers each with Quad core processor and 132 GB memory and is solved using GUROBI solver.

4.2 Effect of vial size and session size on OVW

Based on the average OVW per session obtained from the BIP method in the above experiment, we observe relationship between OVW and vial size for a given session size and, relationship between OVW and session size for a given vial size. Figure 4.2 shows a monotonic increase in OVW as vial size increases for BCG vaccine for session sizes 1, 5, 10, 15 and 20. OVW does not always have an expected inverse relation with session size

Session size	1	2	3	4	5	6	7	8	9-12	13	14	15	16-20	21-50
Measles														
Lee et al. [13]	1 dose vial					10 dose vial								
SOM method	1 dose vial					10 dose vial								
BIP method	1 dose vial					10 dose vial								
Hib														
Lee et al. [13]	1 dose vial					10 dose vial								
SOM method	1 dose vial					2 dose vial		10 dose vial						
BIP method	1 dose vial									10 dose vial				
BCG														
Lee et al. [13]	10 dose vial							20 dose vial						
SOM method	10 dose vial												20 dose vial	
BIP method	10 dose vial													20 dose vial
DTP-HepB-Hib (Pentavalent)														
Lee et al. [13]	1 dose vial					10 dose vial								
SOM method	I dose vial						2 dose vial		10 dose vial					
BIP method	1 dose vial										10 dose vial			

Figure 4.1: Optimal vial sizes for different vaccines when the session size ranges from 1 to 50 children

for a given vial size, as shown in Figure 4.3 for BCG vaccine. Figure 4.3 also shows that the OVW for Measles and BCG vaccines initially increases before exhibiting a monotonic decrease for session sizes of up to 20 for vial sizes of 5 and 10 dose vials for Measles vaccine and, 10 and 20 dose vials for BCG vaccine. The initial increase in OVW can be explained by the stochastic nature of demand. A slight increase in session size from 1 participant per session results in opening of larger number of vials without a significant increase in arrivals. Hence the OVW increases initially with increase in session size. The results from SOM method to study the effect of vial size and session size on OVW showed siimilar trends as that of BIP method.

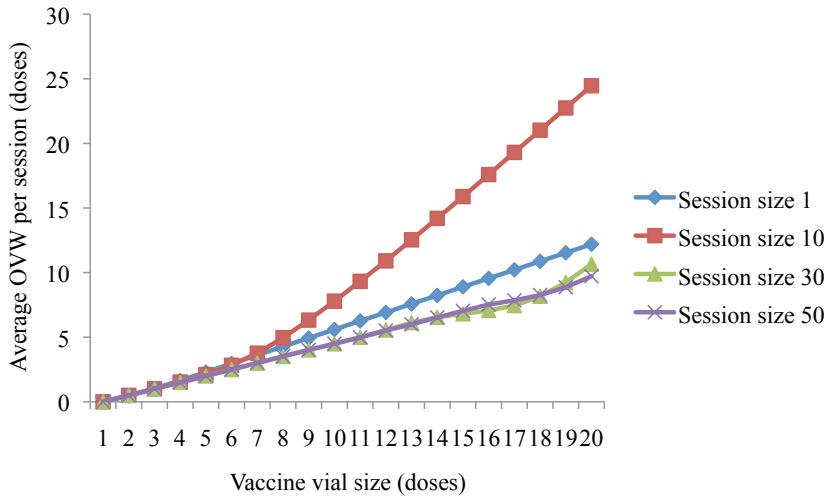

Figure 4.2: A plot of the OVW and the vial size for different session sizes for BCG vaccine

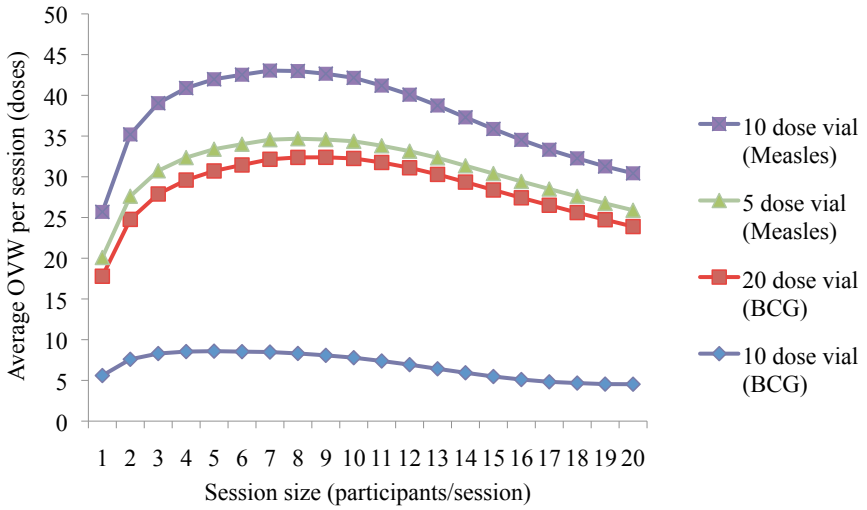

Figure 4.3: A plot of the OVW and the session size for different vial sizes for BCG vaccine

4.3 Effect of session size on optimal cost incurred by VDS per participant

In the third experiment, we study the effect of session size on optimal cost incurred by VDS per child immunized by VDS. The results from the first experiment show us optimal vial size for various session sizes for Measles, Hib and Pentavalent vaccines compute by SOM method. The expected cost computed by the SOM method for these optimal vial sizes for session sizes ranging from 1 to 50 are plotted against session size. Figure 4.4 shows that the optimal immunization cost per child for all three vaccines decreases consistently with increase in session size. Results from BIP method for this experiment showed similar decrease in optimal immunization cost per child with increase in session size. VDS planners may consider the option of increasing the expected session size to a target session size that will reduce the cost incurred by the VDS, by providing incentives to a participant who brings a child to the session. We suggest that the maximum incentive that may be provided per participant is the difference in the optimal immunization cost per child for the expected session size and the targeted session size. Table 4.3 suggests that, for example, in case of Measles vaccine, to attain a target session size of 10 children per day from an expected session size of 3 children per day for the VDS, $1.19 can be provided as an incentive per participant and so on. Since the incentives are based on immunization cost per child, incentives in case of inexpensive vaccines such as BCG vaccine are negligible.

4.4 Effect of purchase cost per session on Q^*

In the fourth experiment we analyze the effect of the purchasing cost per dose for the Measles vaccine on optimal vial size for session sizes 2 and 5 children per session at VDS using SOM method. Based on the purchase

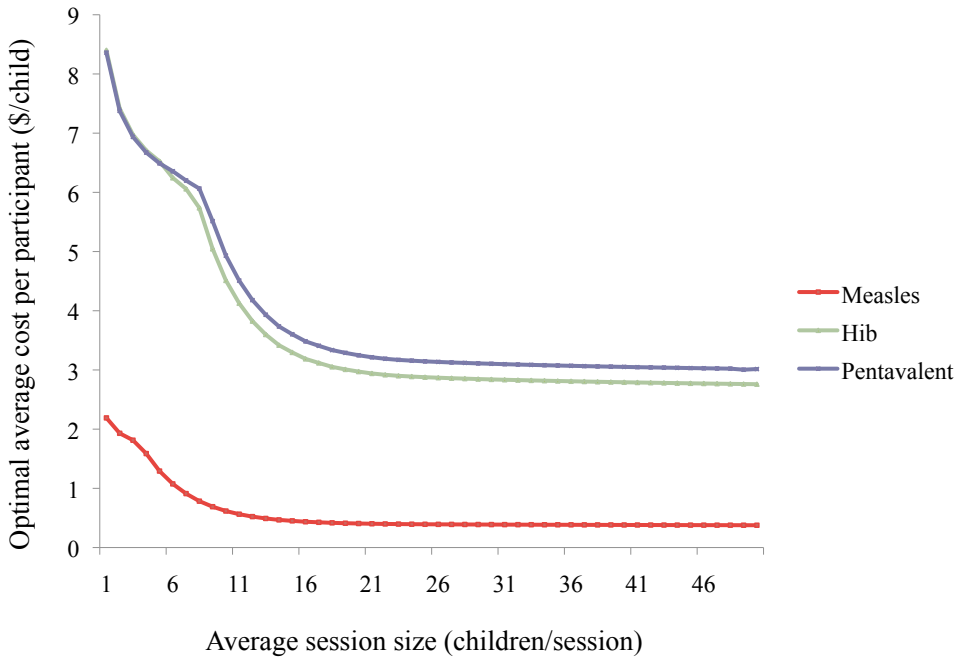

Figure 4.4: A plot of the optimal immunization cost per child and session size for Measles, Hib and Pentavalent vaccines

cost values for 1, 5 and 10 dose vials for Measles vaccine, obtained from [10], we obtained a line of best fit given by *$(1.02-0.0787 Q)*, that represents the purchase cost for Measles vaccine as a function of vial size. Hypothetical cost functions were obtained by changing the intercept *a=1.02* of the Measles cost function, while having a constant slope *m = 0.0787*. Figure 4.5 shows that the optimal vial size for session size of 2 children per day changes from 1 to 10 dose vial when *a* has the value of *$0.92* and the optimal vial size for demand rate of 5 children per day changes from 10 to 1 dose vial when *a* has the value of *$1.32*. Result from BIP method shows the same trend in optimal vial size as observed in this experiment.

Table 4.3: Estimate of maximum incentives that can be offered to the participants

Expected session size (children per day)	Target session size (children per day)	Estimated incentive per participant ($)		
		Measles	Hib	Pentavalent
3	10	$1.19	$2.46	$2.00
3	12	$1.29	$3.15	$2.76
3	14	$1.35	$3.56	$3.2
3	16	$1.38	$3.79	$3.45

VDS with average session size of 2					
Intercept value	$1.02	$0.97	$0.92	$0.87	$0.82
Optimal vial size	1 dose vial		10 dose vial		
VDS with average session size of 5					
Intercept value	$1.02	$1.12	$1.22	$1.32	$1.42
Optimal vial size	10 dose vial			1 dose vial	

Figure 4.5: Effect of purchase cost function on optimal vial size for Measles vaccine

4.5 Optimal vial size for Bangladesh

In the fifth experiment, the data observed during a vaccine wastage study conducted in Bangladesh [8] in the year 2004, on outreach session sizes for BCG and Measles vaccine is used. The observed session sizes are assumed to represent the the session sizes of a VDS. The observed session sizes for both BCG and Measles vaccines are used to fit into a Poisson distribution with a mean of 3 participants per outreach session. Figure 4.6 shows the plot between the average cost per session and the vial size for BCG and Measles vaccines using BIP methos. The purchase cost for vial sizes are obtained by interpolating values from Table 4.2. Single dose vial is recommended as the optimal vial size for BCG and Measles vaccines. When the vaccine study was conducted in Bangladesh, 20 dose vials were used for BCG vaccine and 10 dose vials were used for Measles vaccine. From

the BIP method, the average OVW was found to be 97.9% for 20 dose vial BCG vaccine and 82.9% for 10 dose vial Measles vaccine. Using single dose vials would have eliminated OVW and reduced the average cost per session by 75.8% for BCG vaccine and by 24.4% for Measles vaccine. The results from SOM method also recommended single dose vials for BCG and Measles vaccines.

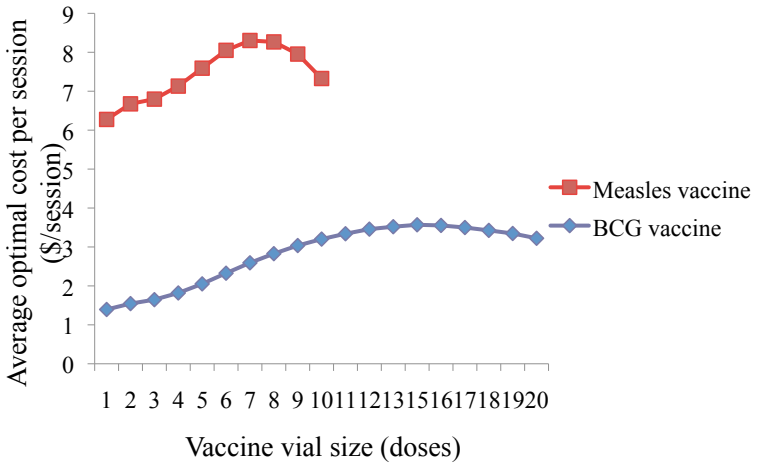

Figure 4.6: A plot between the average cost per session and the vial size for BCG and Measles vaccines based on session size data in Bangladesh [8]

4.6 Tradeoff in solving BIP

Since the BIP method discretizes the planning horizon into fixed number of periods, the parameter b, length of a period, affects the accuracy of the optimal cost obtained from the method and the time taken to solve the method. In this experiment, we consider a 20 dose vial BCG vaccine for a Poisson demand with expected arrival rate of 50 per session, to study the effect

of parameter b on BIP method. For small values of b, we obtain accurate results from BIP method. For larger values of b, the BIP computes approximate OVW which is reflected in the optimal cost computed by BIP method. However, solving BIP method for smaller values of b takes a long time. Figure 4.7 shows the plot of maximum time taken to solve the BIP method in the primary vertical axis and, the plot of accuracy of solution computed by BIP in percentage in secondary axis when b is varied from 1 minute to 5 days. From Figure 4.7, the 30 minute long period is found to be the best choice for the parameter b, for this experiment, as the maximum deviation in average cost from 1 minute long period is less than 4% and the difference in maximum time taken to solve this method between the 30 minute long period and the 5 days long period (fastest to solve) is 90 seconds.

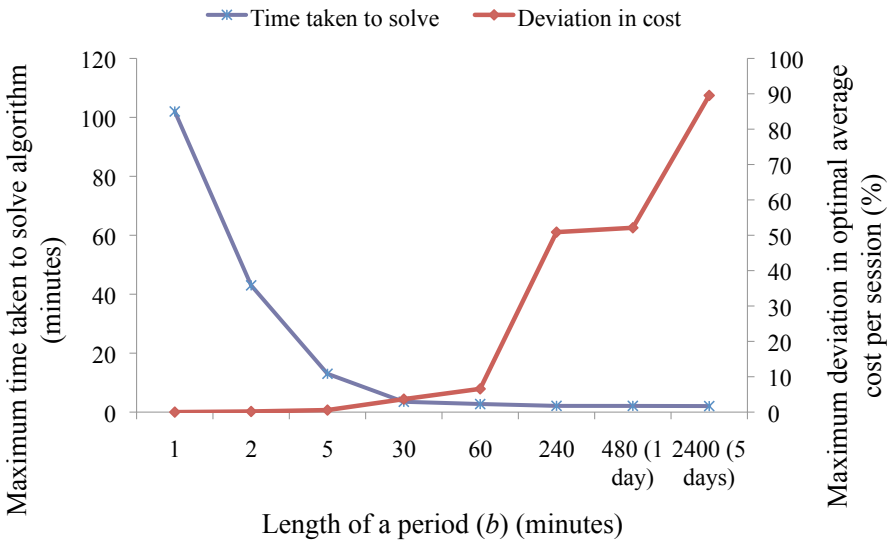

Figure 4.7: A plot between the maximum time taken to solve the BIP method for a session size and maximum difference in optimal cost per session between different values of length of period and 1 minute long period versus the length of a period

Chapter 5

Conclusions and Future Work

In this thesis we propose two methods that could be used as planning tools for a VDS that plans for immunization sessions in rural areas of developing countries. The contribution of the proposed methods is that they consider stochastic demand and provide the best trade-off between vaccine purchase and holding costs on one side and vaccine wastage cost due to OVW on the other side. The BIP method seems to provide better estimates of the optimal costs and the optimal reorder points for shorter lengths of period b. The accuracy of optimal cost and reorder point computed by the SOM method is independent of user defined parameters. Computing resource required to solve the stochastic optimization model is very less compared to the resource required to solve the BIP. However, note that the stochastic optimization model is restricted to Poisson demand and the BIP is designed to handle all types of demand distributions. In order to apply the proposed methods for a VDS that plans for multiple immunization sessions every day, we need data on session sizes organized by a vaccine store in a developing country, which is not found in the literature. Based on experiments conducted in this study, we observe the following five conclusions.

First, single dose vials are usually optimal for smaller session sizes. For a given session size, OVW always increases with increase in vial size. Secondly, session size and purchase cost function are the two most important factors that affect the optimal vial size. Thirdly, for a given vial size, OVW

tends to initially increase with increase in session size and then decreases; the immunization cost per child incurred by a VDS decreases with increase in session size. Fourthly, the VDS planners could use this decrease in the immunization cost per child to provide incentives to participants of an immunization session, in order to increase the session size. Finally, based on session size data in literature, we recommend the use of single dose vials for BCG and Measles vaccines in UVSs of Bangladesh.

Future work should study the lot sizing problem of expensive pharmaceutical products with OVW such as insulin bottles [5]. Future work should generalize the stochastic optimization model, currently restricted by the use of Poisson demands. The methods proposed in this study recommend vial sizes for a vaccine store in a lower echelon of the vaccine distribution system of a country. Future work should extend these methods to recommend vial size for a national level vaccine store. For a given vaccine, the proposed methods restrict VDS to use a single vial size during the planning horizon. Future work should model the impact of using different vial sizes for the same vaccine on OVW and on the transportation cost incurred in the vaccine supply chain of a country. Another direction of research should propose scheduling models for immunization sessions planned by a vaccine store, considering stochastic demand and constrained resources such as health workers and transportation facilities to outreach sites available for immunization.

Appendix A

Extension of both the proposed methods

Both the proposed methods in this study can be extended for a VDS that plans multiple outreach sessions per day and drop-in center sessions during a planning horizon. Consider a VDS that plans for s outreach sessions and a drop-in center session every day of a planning horizon. In case of SOM method, the VDS deals with $(s+1)$ independent demand processes during the planning horizon, each following a Poisson distribution. The modified SOM method for computing optimal vial size and optimal reorder point is shown as a flowchart in Figure A.1.

In case of BIP method, the VDS deals with $(s+1)$ independent demand processes each following different demand distribution during the planning horizon. For a given vial size, the demand generator has to be run separately for $(s+1)$ different distributions. For a given period, the number of vials to be opened, the demand and the OVW computed by the demand generator for $(s+1)$ immunization sessions should be added and used as input to the BIP. The BIP solves for optimal cost and optimal reorder point for a given vial size. The procedures for computation of number replications for which the demand generator and the BIP should be repeated remains the same. Also the procedure to average optimal cost, average optimal reorder point and the optimal vial size remain the same.

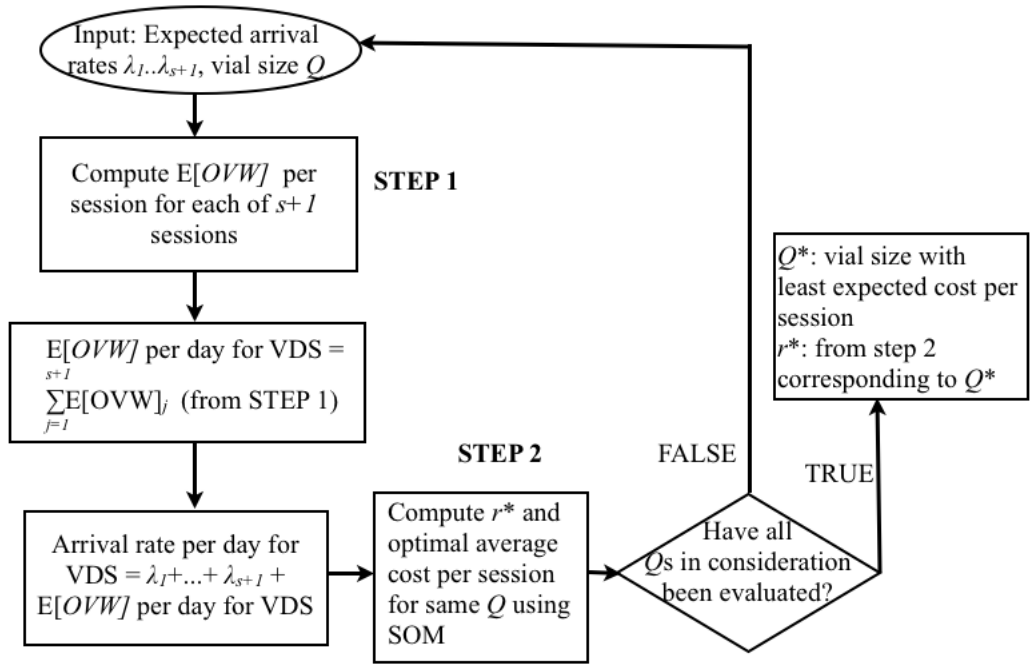

Figure A.1: Flowchart describing modified steps involved in the proposed SOM method

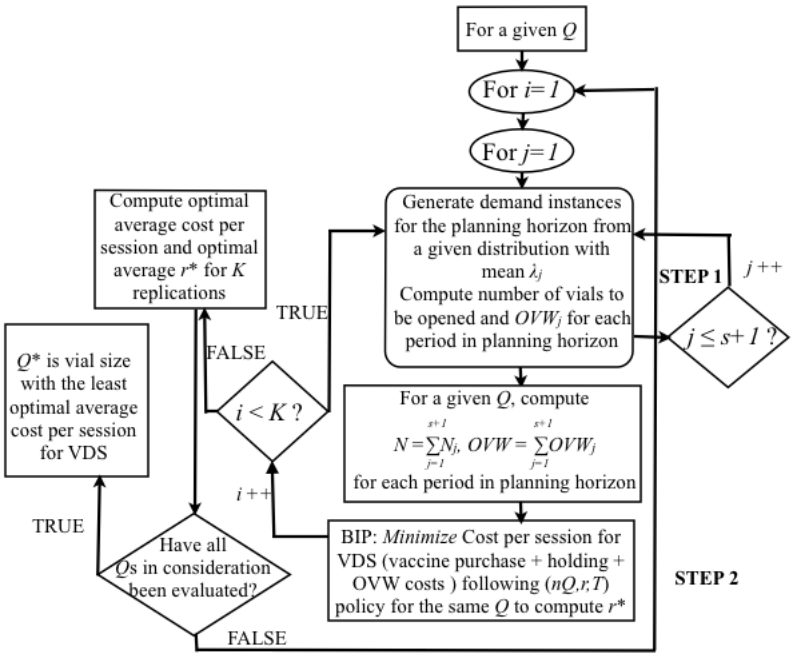

Figure A.2: Flowchart describing modified steps involved in the proposed BIP method

Appendix B

Demand generator algorithm

Parameters:
seed: seed value used in random number generator
Q: vial size (doses/vial)
λ: demand rate also referred as session size (participants/day)
U: planning horizon (days)
n: estimate of maximum number of participants during the planning horizon of VDS
B: number of working minutes in a day (minutes)
b: length of a period (minutes)
P: total number of periods model is run for, $\frac{\text{UB}}{\text{b}}$
τ: OVL of product (number of periods), $\frac{\text{OVL in days B}}{\text{b}}$
x_i: inter-arrival time of i^{th} participant (minutes)
y_i: arrival time of i^{th} participant since the beginning of the planing horizon (minutes)
d_i: demand in i^{th} period (doses)
l_i: number of doses in an open vaccine vial at the beginning of i^{th} period (doses)
N_i: number of vials opened at the beginning of i^{th} period (vials)
W_i: OVW at the end of i^{th} period (doses)

Demand generator:
Begin

$y_1 := x_1 := -\frac{B}{\lambda}\, log(Uniform(seed))$
$While\ i\ in\ 2..n\ Do$

$if\ y_{i-1} > bP\ then$

$exit$

$else$

$x_i := -\frac{B}{\lambda}\, log(Uniform(seed))$

$y_i := y_i - 1 + x_i$

f:=t:=1
$While\ t \leq\ P\ and\ f \leq n\ Do$

$if (t-1)b \leq y_f < tb\ then$

$d_t := d_t + 1$

$f := f + 1$

$else\ t := t + 1$

$While\ j\ in\ 1..(\tau - 1)\ Do$

$W_j := 0$

$While\ k\ in\ 1..P\ Do$

$if\ k\ mod\ \frac{B}{b} = 1\ then$

$l_k := 0$

$N_k := \lceil \frac{d_k}{Q} \rceil$

$else$

$$
\begin{aligned}
& l_k := l_{k-1} + N_{k-1}Q - d_{k-1} - W_{k-1} \\
& if\ d_k > l_k\ then \\
& \qquad N_k := \lceil \frac{d_k - l_k}{Q} \rceil \\
& else\ N_k := 0 \\
& if\ k\ mod\ \frac{B}{b} \geq \tau\ and\ N_{k-\tau+1}Q - \sum_{t=0}^{\tau-1} d_{k-t} - l_{k-\tau+1} \geq 1\ then \\
& \qquad W_k := N_{k-\tau+1}Q - \sum_{t=0}^{\tau-1} d_{k-t} - l_{k-\tau+1} \\
& else\ W_k = 0 \\
& if\ k\ mod\ \frac{B}{b} = 0\ then \\
& \qquad W_k = l_k + N_kQ - d_k \\
End &
\end{aligned}
$$

The demand generator described above generates demand, computes the number of vials opened and the OVW for every period of the planning horizon of the VDS. In the first step of the demand generator, random inter-arrival times of the demand for VDS, for the entire planning horizon are generated. The arrival times of each demand since the beginning of the planning horizon are then calculated. The demand for each period in the planning horizon is generated based on the length of a period *b*. The OVW of vaccine doses is computed and accounted in the vaccine inventory of a VDS for every period, thus different from SOM method that accounts in the inventory for an expected OVW. Since the unused vaccine doses from an open vial at the end of a day or a session are considered wasted, the number of doses from an open vial in the inventory *l*, for the first period of

a day in case of drop-in center session and the first period of an outreach session are assigned zero. The number of vials to be opened N for the first period, corresponds to a ceiling of the ratio between the demand of the period and the vial size. Also W for the final period of a day or a session is computed with a different expression compared to W for all other periods. Since a new vial has to be opened to satisfy the first demand of the day or the session, W for the first $(\tau - 1)$ periods of a day or a session are assigned zero.

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