IMPROVING THE DESIGN AND OPERATION OF WHO-EPI VACCINE DISTRIBUTION NETWORKS

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Vaccines have contributed significantly to the prevention of diseases. Yet millions of children, especially in low and middle income countries, remain unvaccinated and are exposed to preventable diseases such as typhoid, measles and tuberculosis. There are many reasons for this including personal belief systems, vaccine safety concerns, problems with vaccine availability, failures in the healthcare system, social barriers and economic constraints. International organizations are making continual efforts to increase vaccine coverage in these countries using various strategies. In this research we focus on the problems associated with poor design and operation of vaccine delivery systems and address these issues via four broad contributions. First, we present four quantitative models that can be used to optimize the selection of locations for vaccine outreach (where teams from clinics go to relatively remote places to administer vaccines), in order to maximize the number of residents that can be reached; each model addresses a different type of coverage possibility. The models are analyzed and contrasted using an example and adapted to address the situation when the coverage assumptions and demands are uncertain. Second, we propose modular vaccine packaging as an alternative to current packaging, which is not standardized and leads to inefficiencies when packing vaccines into a storage

device; this in turn can result in vaccine shortages. We illustrate the benefits of modular packaging over current packaging schemes and storage devices that are commonly used in the field. Third, we suggest alternative ordering policies at the clinic level that are based on secondary vaccine packaging. The policies draw upon lean concepts that have been used in the manufacturing sector to simplify and improve inventory management. Since the ordering units are larger, storage space issues may occur at clinics or during vaccine transportation and the new ordering polices are analyzed in terms of their effect on storage. Lastly, we propose a mathematical model to redesign the vaccine distribution network from a central warehouse to individual health clinics and study algorithms to solve this difficult problem. We propose a hybrid algorithm based on mixed integer programming and an evolutionary strategy. We also describe how to improve the performance of the evolutionary strategy and how to use the results of the evolutionary strategy to reduce the calculation time of the integer programming model.

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1.0 INTRODUCTION

1.1 MOTIVATION AND RESEARCH OBJECTIVE

In 1974, the World Health Organization (WHO) established the Expanded Programme on Immunization (EPI) to ensure that all children have access to vaccines recommended for routine use (Bland & Clements, 1997). In many low and middle income countries, EPI and the Global Alliance for Vaccines and Immunization (GAVI, which was established in 1999 to extend the reach of EPI to the poorest countries) have combined to save millions of lives since the establishment of these programs. According to 2013 WHO data (Immunization coverage, Fact sheet N°378, 2014), world immunization coverage of diphtheria-tetanus-pertussis (DTP3), Polio, Measles, Tetanus and Hepatitis B vaccines is over 80%. Yet, despite improvements in global vaccine coverage during the past decade, there are millions of children in these countries who still do not get the full regimen of childhood vaccines that are routinely given to children in the developed world (GAVI, 2014) and limited resources, competing health priorities, poor management of health systems, and inadequate monitoring and supervision remain as key challenges. An estimated 22.8 million infants worldwide still miss getting basic vaccines.

There are a multitude of strategies that can be used to deliver immunization services and there are two types of doses that can be given - routine or supplemental. The main distinction is that a supplemental dose is “additional” or “extra” to the doses required by the national

immunization schedule and may, or may not, be recorded in the child's immunization record. On the other hand, a routine dose is one that is prescribed according to the national immunization schedule, is administered based on the vaccination history of each individual, counts towards "fully immunized" status, and must be recorded on immunization cards and registers (WHO/UNICEF Guidance Note, 2011).

By taking advantage of technology, low-cost mass production of many vaccines has become possible. However, keeping vaccines available with low costs remains one of the major challenges for vaccine supply chain managers. Most vaccines need to be maintained within a narrow temperature range from the point of manufacture to their use in an immunization session, within what is called the "cold chain," which is essential to vaccine delivery. Many of the challenges of getting vaccines to children result from the poor management or operation of the vaccine supply chain. In particular, poor infrastructure and the constraints of the cold chain cause inefficiency in vaccine storage and transportation (Zaffran, 1995, Yadav, Lydon, Oswald, Dicko, & Zaffran, 2014).

In many low and middle income countries supported by EPI, vaccines are distributed via their legacy medical supply chain, which is typically a three, four or five tier hierarchical network. Vaccines are purchased by international organizations and delivered to a central distribution center within each country from multiple suppliers/manufacturers. Through various levels of the supply chain, vaccines are then delivered to clinics where the final recipients are located. For example, Niger has a four-tier structure: central store, regional stores, district stores and clinics. All vaccines come to the central store by air and are transported to children successively through regional stores, district stores and finally, clinics. Figure 1 shows the health facilities for Niger. Vaccines are periodically replenished at each facility in amounts that can

ensure adequate service until the next replenishment. In most countries, for locations that are not conveniently located near a clinic, vaccination outreach activities are used, where health workers visit such locations. Since each clinic has very limited resources, including health workers, storage devices, transportation resources and time, teams from the clinic conduct outreach on fixed days in selected locations by foot, or by using locally available means of transportation (bicycles, locally arranged transport, etc.) (Ministry of Health, Government of Southern Sudan, 2009).

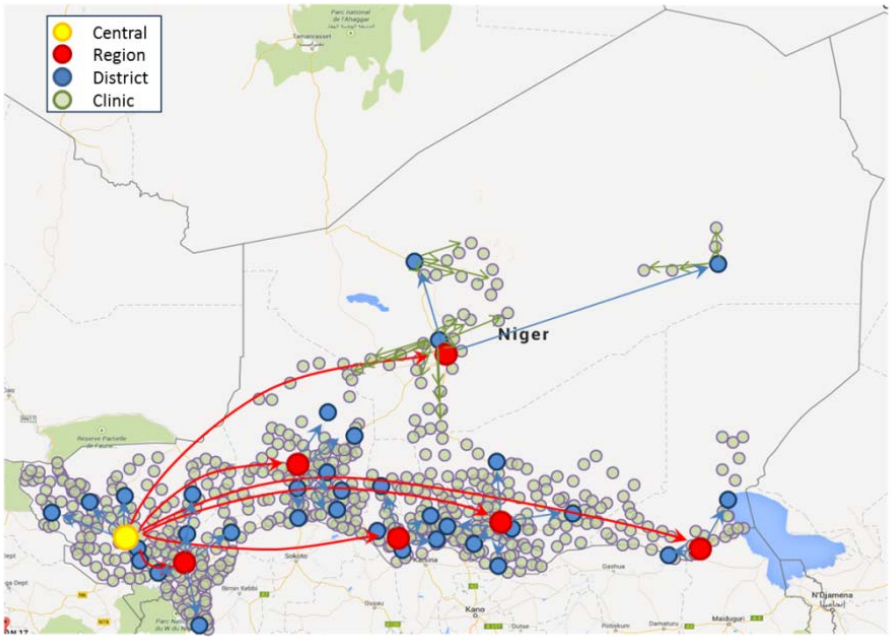


Figure 1. Health facilities for Niger

This study is motivated by the need to seek improvements in vaccine supply chains and ultimately, to have more children be able to have access to vaccines via efficient network flow and scientific management. It begins by studying the issue of outreach. Since outreach sessions are usually not provided at the same location more than once a month and are planned and

organized with the community, they should be arranged such that they cover as many children as possible during the limited number of sessions. This study introduces several vaccine outreach models with different assumptions based on the maximal coverage location problem and investigates the results.

The second focus of this research is on certain logistics aspects of vaccine delivery. Specifically it examines issues associated with storing vaccines efficiently in a storage device when transporting them, and on handling the replenishment process at facilities. When an upper level distribution center or hospital prepares the vaccines to send to lower level distribution centers or clinics, they are often sent in inner packs, which constitute a secondary packaging mode for vaccines. These inner packs are the units in which vials are stored within larger cartons and because of their irregular sizes they can lead to inefficient space utilization within a storage device. This study is designated to clarify the benefits of the modular vaccine packaging which is proposed in Chapter 3. In related work, a vaccine ordering policy is also studied. Currently, at a clinic where actual vaccination occurs the vaccines are ordered in vial units. However, counting several kinds of vaccine vials and ordering them can lead to errors in the ordering process and increases ordering and order fulfillment effort. An ordering policy that is based on using inner pack quantities is proposed that can reduce ordering errors and order fulfillment effort.

In the third part of this research, the problem of redesigning a whole vaccine supply chain is studied. Currently, in many countries vaccines are distributed via their legacy medical supply chain which is typically not cost-efficient. Because vaccines require a cold supply chain, capacity constraints on cold storage and cold transport are critical. Redesigning the vaccine supply chain includes: choosing intermediate hubs among the current distribution center locations, determining the flow paths from the central distribution facility (where vaccines are

received into a country) to health clinics where vaccination actually occurs, the transportation vehicles to allocate to each flow path, and storage devices to use at each location. The re-designed network does not have to follow the current three or four tiered strictly arborescent structure commonly found in practice but can use alternative network structures. To re-design this network, we develop a mixed-integer optimization model and also suggest heuristic methods to get an approximate solution for larger problems. Numerical results are presented using real data from different countries.

1.2 CONTRIBUTIONS

This dissertation develops models for analyzing the issues raised above. The major contributions are:

- The formulation and solution of mixed integer programming (MIP) models for vaccine outreach at the clinic level.
- Robustness analysis on outreach MIP models with respect to uncertain demand in outreach locations and uncertain coverage assumptions.
- Development of a spreadsheet model that evaluates the impact of different modular packing schemes and uses data from the Benin and Niger routine regimen along with commonly used vaccine carriers.
- Applying lean concepts that have been used in the manufacturing sector to vaccine inventory management, in order to simplify ordering procedures and evaluate the impact on storage and transportation resources.

- Creation of a MIP model for redesigning the WHO-EPI vaccine distribution chain in any country and developing a hybrid evolutionary strategy /MIP algorithm to solve the model.
- Development on an algorithm to apply vehicle routing strategies to a vaccine distribution network.

2.0 COVERAGE MODELS TO DETERMINE OUTREACH VACCINATION CENTER LOCATIONS IN LOW AND MIDDLE INCOME COUNTRIES

2.1 INTRODUCTION

Vaccine delivery in many low and middle income countries is an extremely complex problem. The supply chains in such countries are limited in their cold-storage capacity and in their ability to transport vaccines quickly to various points throughout the country. In addition to these supply chain limitations, most of these countries have geographically dispersed or nomadic populations. Portions of their populations have limited or no access to vaccination locations due to poor infrastructure (poor road conditions or limited transportation) or other geographic barriers. As examples, in the country of Niger, 90% of the roads are unpaved (Blanford, Kumar, Luo, & MacEachren, 2012). In Nigeria, people from some rural areas may have to walk at least 26 miles to access health care (BBC, 2006). In Kenya, 40% of the population must travel in excess of an hour to the nearest primary healthcare facility (Noor, Amin, Gething, Atkinson, Hay, & Snow, 2006). Thus, people from remote locations within resource-deprived countries have difficulty reaching immunization locations for their standard regimen of vaccines. This puts these individuals at a very high risk of mortality from infectious diseases such as measles, yellow fever, polio and tuberculosis.

One method to overcome this challenge is to use *outreach*. Sustained outreach is a strategy for reaching remote sections of the population with limited access to immunization locations. With this service, health care workers take vaccines from a fixed immunization location and travel to the remote locations, to immunize individuals there. This service is different from a *campaign* which is a one-time attempt to raise immunization rates. Outreach is extremely important to the overall immunization programs in resource-deprived countries. Without outreach, many countries would suffer from extremely low coverage rates. For example, a study was carried out in three zones of different population densities within Kenya to test the effectiveness of outreach programs as compared to only utilizing fixed immunization locations. The study showed that with outreach, the coverage rate increased from 25% to 57% in the zone with lowest population density. Coverage increased from 54% to 82% in the zone with greatest population density (World Health Organization, 1997).

Outreach is typically provided on a systematic basis, at regular time intervals and regular outreach locations. However, the outreach activities conducted from each immunization location can vary greatly depending on financial resources, time constraints, vaccine availability, population characteristics, usage rate of the fixed immunization location, health worker training, portable cold chain equipment available, and transportation available. The decisions about when and where to conduct outreach and which vaccines to administer, are often made locally, depending on each location's available resources (World Health Organization, 2001).

Outreach from health centers constitutes the critical final link in the vaccine supply chain, which can be quite complex and is typically comprised of four levels in addition to outreach: a central location where vaccines are received into the country from manufacturers, regional locations (typically five to 10) that serve as distribution hubs, districts (typically 25-100) which

serve as the next layer of distribution and where vaccination may occur, and immunization health centers (typically 100-2000) which provide vaccinations to patients (Kaufmann, Miller, & Cheyne, 2011). Outreach planning has a significant effect on the behavior of the entire vaccine distribution chain. As previously noted, in many countries successful outreach greatly increases the number of people vaccinated and therefore increases the number of vaccines that must flow through the entire vaccine supply chain. Thus, it is vital that countries consider the design and intended operation of their outreach programs as they are designing and equipping their entire vaccine supply chain.

In summary, vaccine delivery is a complicated problem and the effectiveness of delivery is critical to reducing mortality rates in many resource-deprived countries. To increase effectiveness outreach is widely utilized. However, there are no quantitative outreach planning models available to help countries and individual facilities plan the optimal outreach strategy. The purpose of this chapter is to address this need.

2.2 PROBLEM DEVELOPMENT AND LITERATURE REVIEW

The objective in each of the various models formulated in this chapter is to maximize the number of people vaccinated through outreach, when resources are limited. We assume that outreach is necessary whenever one or more villages are more than a distance d_1 (typically, 5 km as per WHO guidelines) (Dicko, 2013) from an existing Immunization Health Center (IHC or clinic). An outreach team from the IHC visits one or more such villages, and residents from that village and all villages that are within a distance d_1 of it are able to go there to be vaccinated. We refer to a village that serves as an outreach vaccination center as a "center" and the other nearby

villages (within distance d_1) from which residents travel to the center as "satellite" villages. The maximum number of centers that can be selected for outreach during the planning horizon depends on the financial and other resources available at the IHC. The objective is to select centers so as to maximize the number of residents that can be served at each of the central villages and its respective satellite villages.

As an illustrative example, Figure 2 shows seven villages (represented by the small circles) located near an IHC along with their corresponding patient populations (represented by the numbers above the circles). Three options are shown for the selection of an outreach center from that IHC. If village A is selected as the center [Case A], then the satellite villages that are within 5 km are villages B, C, and D, and thus people in villages A, B, C and D can be vaccinated. People in villages E, F and G will not be vaccinated. In this case, the number of residents that can be covered by outreach is 170. Similarly, 180 people can be covered in Case B and 160 in Case C. Therefore, if we are restricted to a single outreach location, then among these three villages, B would be the best option for a center.

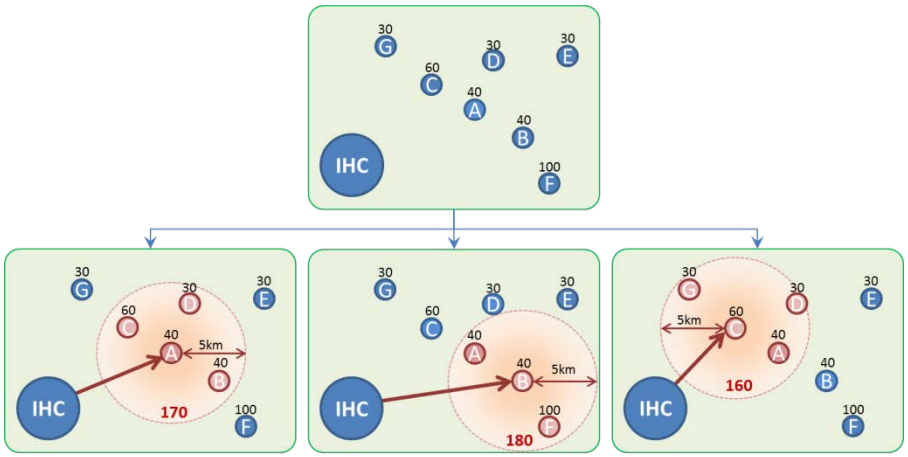


Figure 2. Outreach example: selecting an outreach location

While more than one outreach strategy might be possible, there will typically be constraints that limit the final choice of outreach options. For example, outreach to a particular location has a cost associated with it (that might depend upon distance or terrain or equipment used) and there might be some overall budget for outreach that constrains our choice of outreach trips. Alternatively, costs might be similar for outreach to different sites but we might have a direct limit on the number of outreach sessions (e.g., because of personnel, vehicle, or equipment limits). In other cases, there might be limits on the length of a trip or preferences for certain trips over others. Different strategies are possible depending on these constraints and the assumptions made on the type and amount of patient coverage that can be obtained at a center.

In this chapter, we introduce three models that have different coverage assumptions and an integrated model for multiple IHCs. In addition, we consider the robustness of our solutions with respect to coverage assumptions and uncertainty in demand.

Daskin and Dean (2004) discuss how the location set covering model, maximal covering model and *P*-median model have been used for location planning in health care and review other models derived from these three basic facility models. The different model types are applied selectively according to a problem's characteristics and objective. The problem addressed here may be viewed as a covering problem, which is well-known among facility location models (Farahani, Asgari, Heidari, Hosseininia, & Goh, 2012). In particular, it is related to the Maximal Covering Location Problem (MCLP), which was developed by Church and ReVelle (Church & ReVelle, 1974), with the objective of maximizing the amount of demand covered by a facility. In this model, it is assumed that all demand is covered if the demand location is within an acceptable service distance, otherwise it is not, i.e., coverage is binary. An extension to this is the concept of partial coverage, in which there are two distances: the maximum full coverage

distance D_1 and the minimum non-coverage distance D_2. The demand within distance D_1 from a facility is fully covered while none of the demand beyond distance D_2 is covered. For demand at locations between distances D_1 and D_2 from the facility, the coverage level is assumed to be a decreasing function of the distance to the demand location. Thus, some customers are fully covered and the others are partially covered (Berman & Krass, 2002). This variation has been called the gradual covering problem by Drezner, Wesolowsky, and Drezner (2004), or MCLP with partial coverage by Karasakal and Karasakal (2004). Berman and Krass (2002) collectively refer to this class of models as the Generalized Maximal Covering Location Problem (GMCLP). In order to apply linear programming, they assume that the function for partial coverage is stepwise decreasing, so that the model is similar to MCLP. In these models, all demand at a location is assigned to the nearest facility, even though there might be two or more facilities near the demand location that are capable of serving the demand. Berman, Drezner, and Krass (2009) introduce the cooperative coverage model where the effect of facilities is combined if there are more than two facilities near the demand location. However, in this model the coverage is once again binary, with a demand location being fully covered if an aggregation of partial coverage possible from nearby facilities exceeds a certain threshold; otherwise there is no coverage. That is, there is no partial coverage of demand points.

2.3 COVERAGE MODELS

In this section, we consider four types of models to optimize coverage from outreach. In all of our models we consider multiple outreach locations that can be selected. We start with a basic model that is similar to the binary MCLP model. The second model extends this by drawing

from the GMCLP approach, with coverage being a stepwise and decreasing function of distance. The third model is a new generalization of the cooperative cover model: rather than being binary, an accumulation of partial coverage becomes the partial coverage of the location. The final model is a larger one that could be viewed as a generalization of any of the first three models. Here we formulate it as an extension of the second one, where each facility is constrained to lie within a given radial distance from one of several specific points (the IHCs).

For ease of exposition, we assume that there is sufficient capacity to vaccinate the people who are targeted by an outreach trip (although it would be a straightforward extension to add in capacity constraints for trips). These models are described in the next four subsections, followed by numerical illustrations of each in the section after that. The illustrations use data that is generated from partial information on the state of Bihar in northern India that was obtainable, and which was the motivating application for this work. We conclude with a discussion and summary of our work in the final section.

2.3.1 Model 1: Binary coverage model

In this basic model, it is assumed that residents in villages within a radius of D_1 km from an outreach center are covered, while residents in other villages are not.

Notation:

n: Total number of villages to be served via outreach from the IHC

p_i: Number of residents living in village i

c_i: Cost of outreach at village i if it serves as an outreach center

d_{ij}: Distance between village i and village j (with $d_{ii} = 0$)

D_1: Maximal coverage distance

C: Available budget for outreach

N: Maximum number of outreach centers that is feasible

$x_i \in \{0, 1\}$: 1 if village i is selected as an outreach center; 0 otherwise

$y_i \in \{0, 1\}$: 1 if village i is covered; 0 otherwise

The mathematical model is as follows:

$$Max \sum_{i=1}^{n} p_i y_i \tag{1}$$

subject to

$$y_i \leq \sum_{j \in S_i} x_j \quad \text{for} \quad S_i = \{j: d_{ij} \leq D_1, j = 1, \dots, n\}, \quad i = 1, \dots, n \tag{2}$$

$$\sum_{i=1}^{n} c_i x_i \leq C \tag{3}$$

$$\sum_{i=1}^{n} x_i \leq N \tag{4}$$

$$x_i \in \{0,1\}, \quad y_i \in \{0,1\}, \quad \text{for } i = 1, \dots, n \tag{5}$$

The objective is to maximize the number of people who are vaccinated by outreach (across all villages selected along with their respective satellites). Constraint (2) ensures that village i is covered only if it is D_1 km or less from any village j which serves as an outreach center (a typical value for D_1 might be 5 km). Constraints (3) and (4) respectively ensure that the available outreach budget and the limit on the number of outreach centers are not exceeded. It is conceivable that only one of these constraints might exist.

2.3.2 Model 2: Variable single coverage model

In this model, it is assumed that the coverage by outreach is a stepwise decreasing function of distance from an outreach center, rather than being binary. Given $D_1<D_2<\ldots<D_K$ and $1=\alpha_1>\alpha_2>\ldots>\alpha_K>0$, coverage is divided into groups:

- If there are centers within distance D_1 of the village, all residents (i.e., a fraction $\alpha_1=1$) go to one such center; else
- If there are centers between distance D_1 and D_2, then a fraction α_2 of the patient population will choose to visit one such center; else
- …
- If there are centers between distance D_{K-1} and D_K, then a fraction α_K of the population will choose to visit one such center; else
- There is no coverage.

A typical example might be $K=3$ with $D_1=5$ km, $D_2=8$ km, $D_3=10$ km, and $\alpha_1=1$, $\alpha_2=0.5$, $\alpha_3=0.2$.

Additional notation is as follows:

D_k: Distance from the outreach center of the k^{th} coverage boundary, $k = 1,2, \ldots, K$

α_k: Coverage fraction attained if the nearest center is between D_{k-1} and D_k km of a village

Instead of the y_i variables of the prior section we now have

$y_{ik} \in \{0, 1\}$: 1 if village i is covered by a center between D_{k-1} and D_k km of it; 0 otherwise

The model is as follows:

$$Max \sum_{i=1}^{n} p_i \sum_{k=1}^{K} \alpha_k y_{ik} \tag{6}$$

subject to

$$y_{ik} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j: D_{k-1} \leq d_{ij} \leq D_k, j = 1, \dots, n\}, \;\; i = 1, \dots, n; \quad k = 1, \dots, K \tag{7}$$

$$\sum_{k=1}^{K} y_{ik} \leq 1 \qquad for \;\; i = 1, \dots, n \tag{8}$$

$$\sum_{i=1}^{n} c_i x_i \leq C \tag{9}$$

$$\sum_{i=1}^{n} x_i \leq N \tag{10}$$

$$x_i \in \{0,1\}, \quad y_{ik} \in \{0,1\}, \quad for\; i = 1, \dots, n, \qquad k = 1, \dots, K \tag{11}$$

In this model the objective is the same as in the previous model but coverage is according to the appropriate coverage fraction. Constraint (7) ensures that y_{ik} can be 1 only if village i is within the appropriate coverage radius from any outreach center. Constraint (8) ensures that village i is assigned to at most one outreach center. Constraints (9) and (10) are the usual budget/resource constraints akin to (3) and (4) in Model 1.

2.3.3 Model 3: Variable multiple coverage model

The third model is a generalization of the second one: villages that are not within the 100% coverage distance D_1 are not restricted to partial coverage by a single center (unless it is the only available choice). Rather, residents who do not visit one such center might choose to visit another one. More specifically, given $D_1<D_2<\ldots<D_K$ and $1=\alpha_1>\alpha_2>\ldots>\alpha_K>0$, coverage follows the following pattern:

- If there are $m_1>0$ centers within distance D_1 of the village, all residents (i.e., a fraction $\alpha_1=1$) go to one such center; else

- If there are m_2>0 centers between distance D_1 and D_2, then a fraction α_2 of the population will choose to visit one such center; a further fraction α_2 of the remaining population will choose to visit another such center; and so on

  …

- If there are m_K>0 centers between distance D_{K-1} and D_K, then a fraction α_K of the remaining population will choose to visit one such center; a further fraction α_K of the remaining population will choose to visit another such center; and so on
- There is no coverage if there is no center within distance D_K of the village

In general, the coverage in a village would be given by

$$\beta = 1 - \prod_{k=2}^{K} (1 - \alpha_k)^{m_k}$$

As an example, with K=3, D_1=5 km, D_2=8 km, D_3=10 km, α_1=1, α_2=0.5, α_3=0.2, m_1=0, m_2=2, m_3=1, the fraction of residents covered would be given by $1-(1-0.5)^2(1-0.2)^1 = 0.80$. Thus, if the village had 100 residents, since there are no centers in the inner circle, 50% (i.e., 50) would go to one of the two centers in the next circle while 50% of the remaining 50 (i.e., 25) would go to the other, and 20% of the remaining 25 (i.e., 5) would go to the center in the outer circle; 20 residents would choose not to go to any center for immunization. To further illustrate the difference between the model in this section and the previous one, consider the Figure 3 with four outreach centers in a region of 20 villages; these centers are located at villages 2, 8, 10 and 14. Suppose that as before α_1=1, α_2=0.5 and α_3=0.2 in both models.

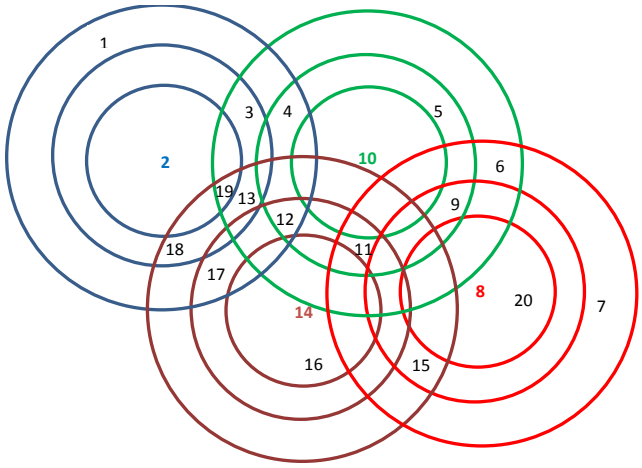


Figure 3. Variable outreach coverage example

Consider village 6 and 11, neither of which is within the inner circle of any center and thus cannot receive 100% coverage. Village 6 is within the outer circles of centers located at villages 8 and 10: with Model 2, the coverage would be 20%, all at one of centers 8 or 10. With Model 3, the coverage would be 36%: 20% at one of 8 or 10, and 16% (i.e., 20% of the remaining 80%) at the other. Village 11 is within the middle circle of the centers at locations 10 and 14 and within the outer circle of the center at location 8. Here the coverage would be 50% with the first model (at either center 10 or center 14), but in the second model with three possible center options, it would be $1-(1-0.5)^2(1-0.2)=80\%$ (50% at one of villages 10 and 14 and 25% at the other, 5% at village 8).

In our formulation of this problem we restrict ourselves to K=3. Define the following additional notation:

M_r: Maximum number of villages within the r^{th} coverage circle of any village, $r = 1,2,3$

$\beta_{m_2 m_3}$: Coverage constant with m_2 centers between (D_1, D_2) and m_3 centers between (D_2, D_3)
$= 1 - (1-\alpha_2)^{m_2}(1-\alpha_3)^{m_3}$

$z_{ikl} \in \{0, 1\}$: 1 if there are no centers located within distance D_1 of i, k centers located between distance (D_1, D_2) of i, and l centers located between distance (D_2, D_3) of village i; 0 otherwise

Instead of the y_{ik} variables of the prior section we now have

$y_i \in \{0,1\}$: 1 if there is at least one center located within distance D_1 of i; 0 otherwise

The values of M_r are determined *a priori* by preprocessing. To illustrate the notation, consider the outreach assignment shown in Figure 2-2. For village 11, we have 0 centers within distance D_1, 2 centers between distance (D_1, D_2), and 1 center between distance (D_2, D_3). Thus $z_{11,2,1}$=1 and $z_{11,k,l}$=0 for all other k, l. For village 19, the corresponding numbers are 1, 0, and 2, but the model will insure $z_{19,k,l}$=0 for all k, l because there is a center located within distance D_1 of village 19.

The model is as follows:

$$Max \sum_{i=1}^{n} p_i y_i + \sum_{i=1}^{n} \sum_{k=0}^{M_2} \sum_{l=0}^{M_3} p_i \beta_{kl} z_{ikl} \tag{12}$$

subject to

$$y_i \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j: d_{ij} \leq D_1, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{13}$$

$$\sum_{k=0}^{M_2} \sum_{l=0}^{M_3} z_{ikl} + y_i \leq 1 \tag{14}$$

$$\sum_{k=0}^{M_2} k \sum_{l=0}^{M_3} z_{ikl} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j: D_1 < d_{ij} \leq D_2, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{15}$$

$$\sum_{l=0}^{M_3} l \sum_{k=0}^{M_2} z_{ikl} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j: D_2 < d_{ij} \leq D_3, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{16}$$

$$\sum_{i=1}^{n} c_i x_i \leq C \tag{17}$$

$$\sum_{i=1}^{n} x_i \leq N \tag{18}$$

$$x_i \in \{0,1\}, \quad y_i \in \{0,1\}, \quad for\; i = 1, \dots, n \tag{19}$$

$$z_{ikl} \in \{0,1\}, \;\; for\; i = 1, \dots, n\,, \;\; k = 0, \dots, M_2, \;\; l = 0, \dots, M_3 \tag{20}$$

The objective in this model has two terms: the first one counts the number of residents in villages with 100% coverage and the second in villages that obtain partial coverage. Constraints (14), (18) and (19) are similar to the ones in the prior models, while (15) ensures that if village *i* gets coverage, it is either 100% coverage or partial coverage from one particular combination of villages in the inner and outer secondary coverage circles. Constraints (16) and (17) along with the fact that β_{kl} is monotone increasing in k and l ensure that z_{ikl} =1 when there are k centers located between distance (D_1,D_2) and l centers located between distance (D_2,D_3) of village *i*.

2.3.4 Model 4: Model with multiple IHCs

In the last model we consider an entire district with multiple IHCs located within it. It is possible that a particular village might be a candidate for outreach from more than one IHC. This model addresses the problem of developing the best combination of outreach programs across all IHCs within a district. We could embed any of the models of the previous section into a larger problem for the entire district as appropriate; here we illustrate the model using the case where there is variable single coverage at each village (as in Model 2). Additional notation is as follows:

m: Number of different IHCs in the district

N_q: Maximum number of outreach activities from IHC q

D_{max}: Maximum travel distance to an outreach location from any IHC

We define y_{ik} similar to what we did in the variable single coverage model but also define

$x_{li} = \{0, 1\}$: 1 if village i is selected as a center for outreach from IHC l; 0 otherwise

The model is as follows:

$$Max \sum_{i=1}^{n} p_i \sum_{k=1}^{K} \alpha_k y_{ik} \tag{21}$$

subject to

$$y_{ik} \leq \sum_{j \in S_i} \sum_{q=1}^{m} x_{lj} \quad for \;\; S_i = \{j : D_{k-1} \leq d_{ij} \leq D_k, j = 1, \dots, n\}, \quad i = 1 \; to \; n \;\; , \;\; k = 1, \dots, K \tag{22}$$

$$\sum_{k=1}^{K} y_{ik} \leq 1 \qquad for \;\; i = 1, \dots, n \tag{23}$$

$$\sum_{i=1}^{n} c_i x_i \leq C \tag{24}$$

$$\sum_{i=1}^{n} x_{qi} \leq N_q \qquad for \;\; q = 1, \dots, m \tag{25}$$

$$d_{qi} x_{qi} \leq D_{max} \qquad for \;\; q = 1, \dots, m, j = 1, \dots, n \tag{26}$$

$$\sum_{q=1}^{m} x_{qi} \leq 1 \qquad for \;\; i = 1, \dots, n \tag{27}$$

$$x_{qi} \in \{0,1\}, \quad y_{ik} \in \{0,1\}, \quad for \; i = 1, \dots, n, \;\; k = 1, \dots, K; \;\; q \; = 1, \dots, m \tag{28}$$

Here *C* represents the budget for the entire district in (25), a separate limit on the number of outreach sessions is defined for each IHC along with a distance constraint for each IHC in (26) and (27), and (28) that ensures that if there is an outreach center at a village it must come from a unique IHC.

2.3.5 Numerical example

We first illustrate the binary, variable single and multiple coverage models with the following example based on the Tetia Bambar IHC in the state of Bihar, India. This IHC has a total of 92

villages in its catchment area that are candidates for outreach centers. We were provided with the distances from the IHC to each outreach village and the patient populations at each village. However, the exact locations of these villages in relation to Tetia Bambar were not available, and given their small sizes and inconsistencies in how their names were spelled it was impossible to accurately locate them on any map. We therefore located the IHC at (0, 0) and randomly assigned coordinates to the villages while maintaining the given distances. The resulting coordinates of the villages along with their patient populations are listed in Table 1.

We use coordinate units of 1 *km* and assume that all distances d_{ij} are Euclidean. For the binary coverage model we assume $D_1 = 5$ *km*. For the variable coverage models, we also assume $D_2 = 8$ *km* and $D_3 = 10$ *km* along with coverage fractions $\alpha_2 = 0.5$ and $\alpha_3 = 0.2$. In order to compare the results across the various models we ignored the budget constraints (i.e., (3), (9), and (17)) because it was impossible to obtain even approximate estimates from Bihar. We only used the constraints on the maximum number of outreach activities (centers), N (i.e., (4), (10), and (18)). We solved each model for increasing values of N until we obtained 100% coverage. For each model, Table 2 lists the coverage obtained for each value of N, along with the respective locations of the outreach centers. The numbers in bold face represent new locations of outreach centers that are added to or replace the ones from the previous (lower) value of N.

The three models often give different locations and levels of coverage when the limit on the number of centers does not allow for 100% coverage. As an example when only 4 centers are possible the coverage is 80.9% with Model 1, 88.6% with Model 2 and 90.5% with Model 3, and the models do not select the same 4 locations. However, as the number of possible centers (and the corresponding coverage) increases the centers start to converge to the same locations. In all cases, a total of 9 centers are required before 100% coverage can be obtained; the locations

are identical and such that each village is within the inner circle (5 *km* radius) of at least one center. Another interesting observation is that while one new center is always added as we increase *N*, there are many instances with all models where in addition to adding a new center an existing location is replaced with a new one. This emphasizes the value of an optimization model in selecting the best strategy. As an example, with Models 1 and 2, when *N* changes from 7 to 8 four of the existing centers are replaced with five new ones; there are only three in common. Similarly, with Models 2 and 3, when *N* changes from 2 to 3, the two existing locations are replaced by three completely new ones.

Table 1. Location information

Village	Location		Population	Village	Location		Population
	X	*Y*			*X*	*Y*	
1	-11.84	4.93	228	47	1.38	-9.63	525
2	-11.03	-7.51	646	48	1.49	5.38	348
3	-10.07	2.85	366	49	1.53	10.24	401
4	-10.07	3.61	671	50	1.84	5.19	706
5	-9.88	0.40	594	51	1.94	4.89	650
6	-9.78	-3.48	624	52	1.97	-5.86	865
7	-8.93	3.79	711	53	2.76	-9.79	624
8	-8.88	2.25	475	54	2.85	3.49	44
9	-7.95	-3.40	198	55	2.92	2.91	147
10	-7.75	-6.21	561	56	3.05	-2.49	563
11	-7.52	0.19	525	57	3.18	5.46	273
12	-7.13	6.73	1,049	58	3.39	-9.66	618
13	-6.25	-2.92	554	59	3.43	-4.51	748
14	-6.07	0.06	496	60	3.96	-7.97	756
15	-5.37	-1.48	701	61	3.97	0.59	508
16	-5.19	3.30	293	62	4.59	-7.89	348
17	-5.14	-5.06	955	63	4.63	1.50	541
18	-4.67	-8.98	466	64	4.65	4.82	240
19	-4.65	11.30	246	65	4.69	2.13	463
20	-4.54	8.41	203	66	5.08	2.93	434
21	-4.38	2.98	297	67	5.29	-2.83	413
22	-4.14	-3.25	398	68	5.59	9.87	848
23	-3.67	0.41	695	69	5.61	-0.88	584
24	-3.60	9.14	254	70	5.76	-5.74	661
25	-3.48	-1.44	160	71	6.00	-0.57	636
26	-3.23	0.92	498	72	6.60	-0.74	682
27	-2.78	-3.86	442	73	6.71	-8.85	646
28	-2.62	-9.70	317	74	6.72	5.99	485
29	-2.38	-6.37	281	75	6.78	-7.45	541
30	-2.36	-2.23	278	76	7.12	1.47	792

Table 1 (continued)

31	-1.74	-8.48	736	77	7.32	0.80	592
32	-1.65	-7.33	566	78	7.47	8.17	573
33	-0.96	3.30	387	79	7.48	6.37	423
34	-0.89	-10.30	195	80	7.70	5.60	493
35	-0.78	-3.81	743	81	7.73	1.48	694
36	-0.71	-3.05	370	82	7.82	-7.71	470
37	-0.62	11.76	553	83	8.05	-6.30	482
38	-0.41	-7.66	272	84	8.14	-1.24	355
39	-0.14	8.26	627	85	8.90	3.83	692
40	0.08	-10.23	543	86	8.94	3.94	677
41	0.24	-8.79	473	87	9.03	0.51	540
42	0.31	-9.84	329	88	9.53	3.62	90
43	0.41	-7.65	374	89	10.03	5.38	613
44	0.62	-10.20	491	90	10.27	6.24	313
45	1.11	6.30	392	91	12.16	-4.61	488
46	1.19	3.24	619	92	12.88	1.33	456

Table 2. Results for the first three models

	Model 1: Binary Coverage			Model 2: Variable single coverage			Model 3: Variable multiple coverage		
N	No. Covered	Percent Covered	Center Locations	No. Covered	Percent Covered	Center Locations	No. Covered	Percent Covered	Center Locations
1	10,749	26.9%	51	14,238	35.7%	53	14,238	35.7%	53
2	20,515	51.4%	**48**, 51	25,167	63.1%	**30**, **51**	25,463	63.8%	**30**, **51**
3	27,417	68.7%	**11**, 48, 51	32,390	81.2%	**11**, **48**, **52**	33,093	83.0%	**11**, **43**, **60**
4	32,257	80.9%	**8**, **17**, 48, 51	35,331	88.6%	**7**, **17**, 48, 52	36,119	90.5%	**5**, **31**, **35**, **62**
5	35,812	89.8%	8, 17, **31**, 48, **62**	37,853	94.9%	8**,** 17, **31**, 48, **62**	38,347	96.1%	**8**, **17**, 31, **48**, **62**
6	37,590	94.2%	8, 17, 31, 48, **60**, **73**	38,742	97.1%	8, 17, 31, 48, **60**, **73**	39,132	98.1%	8, 17, 31, 48, **60**, **73**
7	39,259	98.4%	**6**, 8, **30**, 31, 60, **69** ,**73**	39,572	99.2%	**6**, 8**, 30**, 31, 60, **69**, 73	39,746	99.6%	**6**, 8, **30**, 31, 60, **69**, 73
8	39,666	99.4%	**10**, **11**, **23**, **35**, **39**, 60, 69, 73	39,780	99.7%	**10**, **11**, **23**, **35**, **39**, 60, 69, 73	39,844	99.9%	6, 8, **23**, 30, **39**, 60, 69, 73
9	39,894	100.0%	**8**, 10, **22**, 23, 35 ,39, 60, 69, 73	39,894	100.0%	**8**, 10, **22**, 23, 35 ,39, 60, 69, 73	39,895	100.0%	**8**, 10, **22**, 23, 35 ,39, 60, 69, 73

Finally, it is worth noting that there could be differences in the actual number of people covered at a specific outreach center; some centers that cover more locations might cater to a

larger number of patients than others. However, the imbalances are not drastic. As an illustration, consider the case when we have 6 outreach centers, in which case all three coverage models choose the same set of six locations for outreach as shown in Table 2 (Villages 8, 17, 31, 48, 60 and 73). Table 3 displays the actual population covered at each of these locations under the different coverage models.

Table 3. Coverage at each of 6 centers with different coverage models

Model	Location No.						Total
	8	17	31	48	60	73	
Binary	5,704	6,040	3,592	9,766	6,416	6,073	37,590
Variable Single	5,704	6,490	3,714	9,997	6,416	6,420	38,742
Variable Multiple	5,971	6,425	3,665	10,214	6,526	6,329	39,132

Figure 3 provides a visual summary of the coverage results. Obviously, the variable coverage models always provides higher coverage than the binary coverage model but the differences start to get smaller when the number of centers (N) reaches about 7, and the models are identical when N =9. The two variable coverage models behave similarly, and the gains from multiple coverage (as well as from variable coverage) over binary coverage are more noticeable at intermediate values of N. This is significant because in practice, the values of N are more likely to be in this intermediate range: if N is small the options are limited and the benefits of an optimization model are not significant, while large N values are unlikely in practice because of budgetary considerations and resource constraints. While Figure 4 indicates that we have diminishing marginal gains in coverage as we add outreach sessions, it also allows a social planner to evaluate these gains in light of the extra resources (monetary, equipment, personnel, etc.) that might be required for additional outreach sessions.

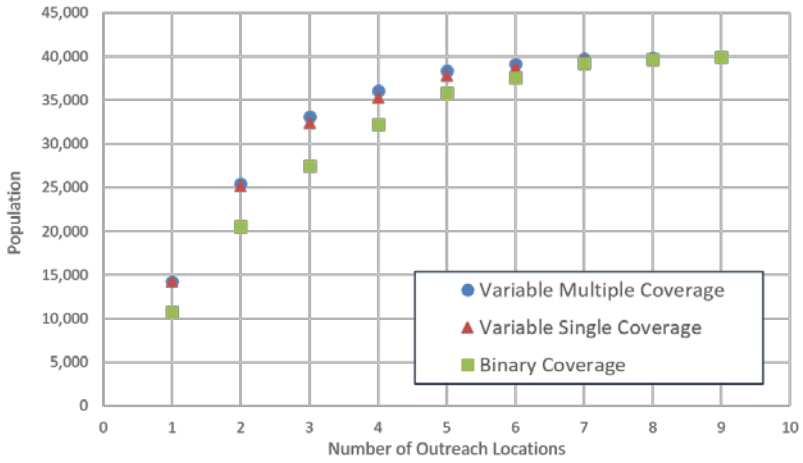
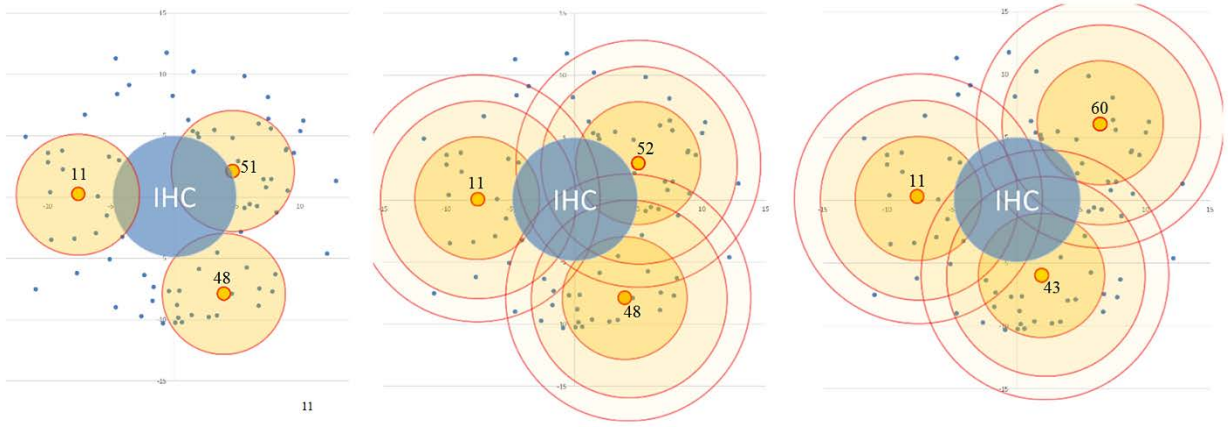


Figure 4. Coverage with first three models

Figure 5 further illustrates the differences in results from the three models for an intermediate value of *N*=3. The three panels in the figure provide a visual depiction of the actual locations selected by the models. Notice that location 11 is common to all three models but the others differ depending on the model in use.



Binary Coverage (*N*=3)
Centers at 11, 48 and 51

Variable Single Coverage (*N*=3)
Centers at 11, 48 and 52

Variable Mutiple Coverage (*N*=3)
Centers at 11, 43 and 60

Figure 5. Locations of 6 centers with different types of coverage

Finally, to illustrate the multiple IHC model consider a hypothetical district with a total of 80 villages served by 4 IHCs. The locations of the villages and the IHCs are depicted in Figure 6. Populations of the individual villages are not shown, but these were randomly generated; the total population of the district for this example was equal to 4,645.

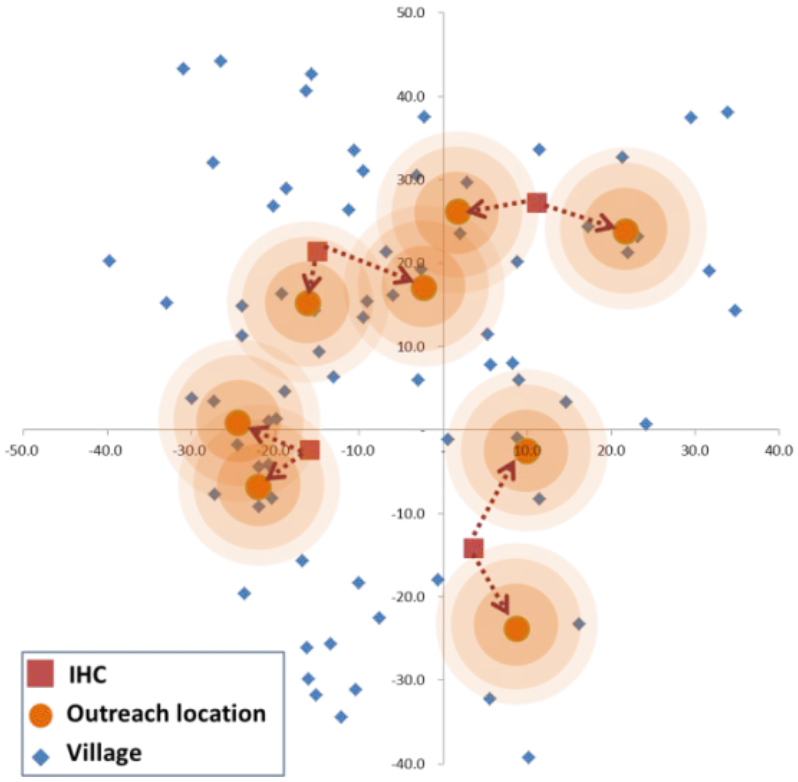


Figure 6. Locations of 8 outreach centers for maximizing coverage

In defining constraint (26) we assume the same value of N_q for all values of q, i.e., that each IHC was restricted to the same maximum number of outreach centers. The multi-IHC problem was solved for values of N_q ranging from 1 through 9; the results on the total coverage are shown in Table 4. Once again budget constraints were ignored for the illustration.

Table 4. Coverage with 4 IHCs

Outreach per IHC	Population	Coverage Percentage
1	1,387	29.9
2	2,243	48.3
3	2,810	60.5
4	3,169	68.2
5	3,416	73.5
6	3,607	77.7
7	3,743	80.6
8	3,816	82.2
9	3,846	82.8

As Table 4 indicates, there is a diminishing marginal benefit from allowing an IHC to have an extra outreach center. In practice the number of outreach centers permissible would be limited by the budget and other available resources, but a table such as this one allows planners to balance the additional resources expended with more outreach centers against the gains in the number of residents vaccinated. Figure 6 illustrates the case where N_q=2 and shows the locations of the two outreach centers for each of the four IHCs; the total coverage here is about 48%.

2.4 ROBUST MODELS

In this section, we consider two types of uncertainty. The first is with respect to our coverage assumptions. The first three models have different coverage assumptions based on the behavior of the underlying population. But it is difficult to know this behavior exactly. If a model that does not reflect the actual behavior of the population is applied, the result would not be reliable,

and the goal is to examine how the results from one set of assumptions perform when the actual behavior is different from the assumed one. The second type of uncertainty is with respect to demand. Since there might be a time difference between when the number of people at a location is recorded and when an outreach activity occurs, the number of people at a location might not be accurate, so that we have to consider possible variation in the number of people that might be served by outreach to see how robust a particular outreach strategy might be.

2.4.1 Robustness for coverage assumptions

Clearly, a solution to one of the models is feasible for the other models, since any set of outreach centers can be a solution. Therefore, we do not need to consider the potential for infeasibility of solutions to a model. Rather, a robust solution will be one that provides a good solution for all three models without sacrificing very many people that need to be covered. Table 5 shows the number of covered people for each model when the optimal solution of each of the other two models is applied. The percentage value shown below the number of covered people is the percentage difference from the maximum number of people covered by any of the models.

Table 5. The number of covered people in each model with the optimal solution of the other models

model	1			2			3		
solution	1	2	3	1	2	3	1	2	3
1	10,749	8,508 (20.85%)	8,508 (20.85%)	14,060 (1.26%)	14,239	14,239	14,060 (1.26%)	14,239	14,239
2	20,515	19,928 (2.86%)	19,928 (2.86%)	24,253 (3.64%)	25,169	25,169	24,253 (4.76%)	25,465	25,465
3	27,418	27,163 (0.93%)	25,985 (5.23%)	32,384 (0.03%)	32,394	32,078 (0.98%)	32,639 (1.38%)	32,840 (0.77%)	33,097
4	32,260	32,005 (0.79%)	29,509 (8.53%)	35,249 (0.24%)	35,335	34,704 (1.79%)	35,442 (1.88%)	35,717 (1.12%)	36,123

Table 5 (Continued)

5	35,816	35,816	35,816	37,857	37,857	37,857	38,351	38,351	38,351
6	37,593	37,593	37,593	38,746	38,746	38,746	39,135	39,135	39,135
7	39,254	39,254	39,254	39,576	39,576	39,576	39,700 (0.05%)	39,700 (0.05%)	39,720
8	39,670	39,670	39,652 (0.05%)	39,784	39,784	39,775 (0.02%)	39,807 (0.07%)	39,807 (0.07%)	39,837
9	39,898	39,898	39,898	39,898	39,898	39,898	39,898	39,898	39,898

These results indicate that choosing the wrong model might result in a significant number of people not being served (e.g., 20.85% in this example when the optimal solution from model 2 is used but the behavior of patients is actually as assumed in model 1.) Note that when we can choose more outreach centers the solutions are the same (or very similar) regardless of the model used, but when we have a limited budget and the number of outreach centers we can have is small wrong assumptions on the population behavior can result in lower coverage. In order to address this issue, a solution that performs well and is robust across all three models is desired and can be found using robustness techniques. That is, in order to obtain a robust solution to all three models, we have to minimize the maximum difference between the number of people who can be covered with each model and the number of people who can be covered with a robust solution. The robust model is as follows:

$$\text{Min } t \tag{29}$$

subject to

$$G_1(N) - \sum_{i=1}^{n} p_i y_i \leq t \tag{30}$$

$$G_2(N) - \sum_{i=1}^{n} p_i \sum_{k=1}^{K} \alpha_k y_{ik} \leq t \tag{31}$$

$$G_3(N) - \sum_{i=1}^{n} p_i y_i - \sum_{i=1}^{n} \sum_{k=0}^{M_2} \sum_{l=0}^{M_3} p_i \beta_{kl} z_{ikl} \leq t \tag{32}$$

$$y_i \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j : d_{ij} \leq D_1, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{33}$$

$$\sum_{i=1}^{n} c_i x_i \leq C \tag{34}$$

$$\sum_{i=1}^{n} x_i \leq N \tag{35}$$

$$y_{ik} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j : D_{k-1} \leq d_{ij} \leq D_k, j = 1, \dots, n\}, \;\; i = 1, \dots, n; \;\; k = 1, \dots, K \tag{36}$$

$$\sum_{k=1}^{K} y_{ik} \leq 1 \quad for \;\; i = 1, \dots, n \tag{37}$$

$$y_i \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j : d_{ij} \leq D_1, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{38}$$

$$\sum_{k=0}^{M_2} \sum_{l=0}^{M_3} z_{ikl} + y_i \leq 1 \tag{39}$$

$$\sum_{k=0}^{M_2} k \sum_{l=0}^{M_3} z_{ikl} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j : D_1 < d_{ij} \leq D_2, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{40}$$

$$\sum_{l=0}^{M_3} l \sum_{k=0}^{M_2} z_{ikl} \leq \sum_{j \in S_i} x_j \quad for \;\; S_i = \{j : D_2 < d_{ij} \leq D_3, j = 1, \dots, n\}, \;\; i = 1, \dots, n \tag{41}$$

$$x_i \in \{0,1\}, \quad y_i \in \{0,1\}, \quad for \; i = 1, \dots, n \tag{42}$$

$$y_{ik} \in \{0,1\}, \quad for \; i = 1, \dots, n, \qquad k = 1, \dots, K \tag{43}$$

$$z_{ikl} \in \{0,1\}, \;\; for \; i = 1, \dots, n \,, \;\; k = 0, \dots, M_2, \;\; l = 0, \dots, M_3 \tag{44}$$

where $G_i(N)$ is the objective value of the model i when the number of outreach location is N

The objective function and constraints (30) – (32) ensure that we minimize the difference between the optimal value in each model and the optimal robust value. Since all three models optimize the number of people covered for a specific value of *N*, there is not a significant issue with objective function scaling in constraints (30) – (32). However, we could consider scaling *t*

depending on the objective of the robustness analysis. For example, if we want to minimize the maximum percentage deviation across the three models from the robust optimum, we can multiply t by $G_i(N)$ (e.g., $G_1(N) - \sum_{i=1}^{n} p_i y_i \leq G_1(N)t$). Constraints (33) – (44) come from models 1, 2 and 3. Table 6 shows the result when the robust solution from the above model is evaluated using each of the three original models, and the numbers in parentheses display the percentage of the population lost as a result of using the robust solution in place of the optimal one. If the outreach centers from the robust solution are used, then for any *N*, the maximum percent deviation from the best possible solution is 1.94%.

Table 6. Result of robust solution for uncertain assumption

N	Model		
	1	2	3
1	10,749	14,060 (1.26%)	14,060 (1.26%)
2	20,117 (1.94%)	25,043 (0.50%)	25,179 (1.12%)
3	27,163 (0.93%)	32,390	32,840 (0.77%)
4	32,005 (0.79%)	35,335	35,717 (1.12%)
5	35,816	37,857	38,351
6	37,593	38,746	39,135
7	39,254	39,576	39,720
8	39,670	39,784	39,825 (0.03%)
9	39,898	39,898	39,898

2.4.2 Robustness for uncertain demand

We can also consider uncertainty in the number of people (=demand) at each village. In this section, we consider a robust version for Model 1. Those for Model 2 and 3 can be expressed similarly.

Let us define the feasible region *A* for Model 1 as follows:

$$A = \{(\boldsymbol{x}, \boldsymbol{y}) | y_i \le \sum_{j \in S_i} x_j \ \text{ for } S_i = \{j : d_{ij} \le D_1, j = 1, \dots, n\}, \ \ i = 1, \dots, n,$$

$$\sum_{i=1}^{n} c_i x_i \le C, \sum_{i=1}^{n} x_i \le N; \ x_i \in \{0,1\}, \quad y_i \in \{0,1\}, \quad for\ i = 1, \dots, n\}$$

Now suppose that $\hat{p}_i$ is an estimate of the population in village i and that $\hat{p}_i \gamma_i$ is the amount by which the true population p_i differs from this estimated value $\hat{p}_i$, so that $p_i - \hat{p}_i = \hat{p}_i \gamma_i$, i.e., $p_i = \hat{p}_i(1 + \gamma_i)$. Also assume that

$\sum_{i=1}^{n} \hat{p}_i \gamma_i = 0$ so that $\sum_{i=1}^{n} p_i = \sum_{i=1}^{n} \hat{p}_i = D$

$0 < |\gamma_i| \le \bar{\gamma}_i < 1$

In other words we know the total population (*D*) across all *n* villages, but the true population p_i at village *i* could be up to $100\bar{\gamma}_i$% higher or lower than its estimated population $\hat{p}_i$.

Let us define the set B as

$$B = \{\boldsymbol{\gamma} | \sum_{i=1}^{n} \hat{p}_i \gamma_i = 0, |\gamma_i| \le \bar{\gamma}_i < 1\}$$

where $\boldsymbol{\gamma}$ is a vector of γ_i.

Robust Model:

$$\max_{\boldsymbol{x}, \boldsymbol{y}} \left\{ \inf_{\boldsymbol{\gamma}} \sum_{i=1}^{n} \hat{p}_i (1 + \gamma_i) y_i \ \middle| \ (\boldsymbol{x}, \boldsymbol{y}) \in A, \boldsymbol{\gamma} \in B \right\}$$

Note that for a given feasible selection of outreach centers ($\boldsymbol{x}$) and corresponding set of villages covered ($\boldsymbol{y}$), the quantity within the braces represents the smallest value of the true total population covered across all different deviations from the estimates that meet conditions 1-3 above. The objective of the model is to find the vectors $\boldsymbol{x}$ and $\boldsymbol{y}$ that maximize this value.

Proposition

If $\bar{\gamma}_1 = \bar{\gamma}_2 = \cdots = \bar{\gamma}_n = \bar{\gamma}$, then the optimal solution to the original formulation (Model 1) is the optimal solution to the robust formulation.

Proof:

Let $(\boldsymbol{x}^*, \boldsymbol{y}^*)$ be the optimal solution to Model 1, and consider any feasible $(\boldsymbol{x}, \boldsymbol{y}) \in A$ and define *C* as the index set of villages that are covered and *N* as the index set of villages that are not covered. Note that C∪*N* = {1,2,…,*n*} and the estimated total coverage is $\sum_{i \in C} \hat{p}_i$ while the estimated population not covered is given by $\sum_{i \in N} \hat{p}_i = D - \sum_{i \in C} \hat{p}_i$.

Define

$$\xi(\boldsymbol{x}, \boldsymbol{y}) = \sum_{i \in C} \hat{p}_i = \sum_{i=1}^{n} \hat{p}_i y_i$$

$$\bar{\xi}(\boldsymbol{\gamma} | \boldsymbol{x}, \boldsymbol{y}) = \min_{\boldsymbol{\gamma}} \left\{ \sum_{i=1}^{n} \hat{p}_i (1 \pm \gamma_i) y_i \;\middle|\; \boldsymbol{\gamma} \in B \right\}$$

Note that for the assignment $(\boldsymbol{x}, \boldsymbol{y})$, $\xi(\boldsymbol{x}, \boldsymbol{y})$ is the estimated total coverage, while $\bar{\xi}(\boldsymbol{\gamma} | \boldsymbol{x}, \boldsymbol{y})$ is the smallest actual total coverage possible across all differences from the estimates that satisfy conditions 1-3 described earlier.

Case 1: $\xi(\boldsymbol{x}, \boldsymbol{y}) = \sum_{i \in C} \hat{p}_i \leq D/2)$

In this case the true total coverage has its minimum value $\bar{\xi}(\boldsymbol{\gamma} | \boldsymbol{x}, \boldsymbol{y})$ when the true population of each village $i \in C$ is $\hat{p}_i(1 - \bar{\gamma})$, as long as this minimum can be attained. This minimum is attained as long as the true total population not covered (in the villages indexed by

set *N*) does not exceed $(1+\bar{\gamma})\sum_{i\in N}\hat{p}_i$, which is the largest possible value that this number can take on.

The true number not covered is given by $D-(1-\bar{\gamma})(\sum_{i\in C}\hat{p}_i)$ and therefore we need to show that $\{D-(1-\bar{\gamma})(\sum_{i\in C}\hat{p}_i)\} \le \{(1+\bar{\gamma})(\sum_{i\in N}\hat{p}_i)\}$. This is easily done because

$\{D-(1-\bar{\gamma})(\sum_{i\in C}\hat{p}_i)\} - \{(1+\bar{\gamma})(\sum_{i\in N}\hat{p}_i)\}$

$= \{D-(1-\bar{\gamma})(\sum_{i\in C}\hat{p}_i)\} - \{(1+\bar{\gamma})(D-\sum_{i\in C}\hat{p}_i)\}$

$= \bar{\gamma}\{2\sum_{i\in C}\hat{p}_i - D\} \le 0$ (because $\bar{\gamma}>0$ and $\sum_{i\in C}\hat{p}_i \le D/2$)

Therefore

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x},\boldsymbol{y}) = \sum_{i\in C}(1-\bar{\gamma})\hat{p}_i = (1-\bar{\gamma})\xi(\boldsymbol{x},\boldsymbol{y}),$$

and in particular, for $(\boldsymbol{x}^*,\boldsymbol{y}^*)$

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x}^*,\boldsymbol{y}^*) = (1-\bar{\gamma})\xi(\boldsymbol{x}^*,\boldsymbol{y}^*)\,.$$

Since $(\boldsymbol{x}^*,\boldsymbol{y}^*)$ is optimal for Model 1, it follows that $\xi(\boldsymbol{x},\boldsymbol{y}) \le \xi(\boldsymbol{x}^*,\boldsymbol{y}^*)$, and therefore

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x},\boldsymbol{y}) \le \bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x}^*,\boldsymbol{y}^*).$$

Therefore $(\boldsymbol{x}^*,\boldsymbol{y}^*)$ is also optimal for Model 2.

Case 2: $\xi(\boldsymbol{x},\boldsymbol{y}) = \sum_{i\in C}\hat{p}_i > D/2)$

Here it is not possible for the true coverage to attain the minimum possible value of $(1-\bar{\gamma})\sum_{i\in C}\hat{p}_i$ because the actual total number not covered would then exceed its maximum possible value. Instead we make use of the fact that the minimum actual coverage is attained when the actual number not covered is at its maximum of $(1+\bar{\gamma})\sum_{i\in N}\hat{p}_i$. To show this minimum can be attained we need to ensure that the true total number covered is larger than $(1-\bar{\gamma})\sum_{i\in C}\hat{p}_i$, which is the smallest value that it can take on.

The true number covered is given by $D-(1+\bar{\gamma})(\sum_{i\in N}\hat{p}_i)$ and therefore we need to show that $\{D-(1+\bar{\gamma})(\sum_{i\in N}\hat{p}_i)\} \ge \{(1-\bar{\gamma})(\sum_{i\in C}\hat{p}_i)\}$. This is easily done because

$$\{D - (1+\bar{\gamma})(\textstyle\sum_{i\in N}\hat{p}_i)\} - \{(1-\bar{\gamma})\textstyle\sum_{i\in C}\hat{p}_i\}$$

$$= \{D - (1+\bar{\gamma})(D - \textstyle\sum_{i\in C}\hat{p}_i)\} - \{(1-\bar{\gamma})\textstyle\sum_{i\in C}\hat{p}_i\}$$

$$= \bar{\gamma}\{2\textstyle\sum_{i\in C}\hat{p}_i - D\} > 0$$

Therefore

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x},\boldsymbol{y}) = D - (1+\bar{\gamma})\textstyle\sum_{i\in N}\hat{p}_i$$

$$= D - (1+\bar{\gamma})\big(D - \textstyle\sum_{i\in C}\hat{p}_i\big) = (1+\bar{\gamma})(\textstyle\sum_{i\in C}\hat{p}_i) - \bar{\gamma}D$$

$$= (1+\bar{\gamma})\xi(\boldsymbol{x},\boldsymbol{y}) - \bar{\gamma}D,$$

and in particular, for $(\boldsymbol{x}^*,\boldsymbol{y}^*)$

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x}^*,\boldsymbol{y}^*) = (1+\bar{\gamma})\xi(\boldsymbol{x}^*,\boldsymbol{y}^*) - \bar{\gamma}D.$$

Since $(\boldsymbol{x}^*,\boldsymbol{y}^*)$ is optimal for Model 1, it follows that $\xi(\boldsymbol{x},\boldsymbol{y}) \leq \xi(\boldsymbol{x}^*,\boldsymbol{y}^*)$, and therefore

$$\bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x},\boldsymbol{y}) \leq \bar{\xi}(\boldsymbol{\gamma}|\boldsymbol{x}^*,\boldsymbol{y}^*). \blacksquare$$

Example:

Suppose we have a total of 100 people in our *n* villages and the true population in any individual village *i* could be higher or lower than the estimated value $\hat{p}_i$ by no more 10% (so $\bar{\gamma}$=0.1).

Case 1: Suppose $\sum_{i\in C}\hat{p}_i$ =45 people are estimated to live in villages covered and $\sum_{i\in N}\hat{p}_i$ =55 in villages not covered. Then the lowest true coverage possible is 45(0.9) = 40.5 with 59.5 people not being covered.

Case 2: Suppose $\sum_{i\in C}\hat{p}_i$ =55 people are estimated to live in villages covered and $\sum_{i\in N}\hat{p}_i$ =45 in villages not covered. Then the lowest true coverage possible is when the actual number not covered is at its maximum of 45(1.1) = 49.5, i.e., with 50.5 people being covered.

According to the previous proposition, the optimal solution to the model without demand uncertainty is the robust solution for uncertain demand. If the assumption about the equality of

the total population is removed, the result is the same because the objective value for all solutions would be decreased by $\bar{\gamma}$. In addition, even if the assumption of percentage deviation from the estimated population is changed to a fixed amount of deviation from the estimated population, the optimal solution is still the robust solution. The fact that the solution to the robust model is the same as the solution for the original model is because of the following characteristics of the coverage model: 1) it maximizes the number of people who can be covered, 2) the robust model provides the optimum corresponding to the worst-case scenario for the error in the estimated population, and 3) there is no systematic interaction between the populations at different locations. Thus, in order to have the best worst-case performance it is optimal to locate the outreach points at the locations that maximize coverage with the estimated populations. This follows because if the population at each location can either be reduced by a constant percentage or a constant amount then the locations that maximizes coverage in the original problem will still provide the highest coverage for the new problem.

2.5 DISCUSSION AND CONCLUSIONS

To the best of our knowledge the work reported here is the first to provide a formal modeling framework for decision making with respect to outreach. As with any model-based approach, our work has some limitations and certain facts are worth keeping in mind. First, our results apply mainly to rural outreach settings with relatively lower population densities; in densely populated urban settings coverage models could clearly be much more complex. However, since most urban centers tend to have health posts or clinics with regular hours, outreach generally *is* focused on rural locations. Second, we assume that the social planner is not biased in favor of

outreach plans where the travel is shorter or across easier terrain (which is sometimes the case in practice), and that the plans from our model can be implemented in an unbiased fashion. Third, in general it could be difficult to predict the exact type of coverage applicable to a particular application environment. However, the models could be run under different assumptions of coverage, and as the results indicate, in many instances the optimal locations are identical (e.g., with N=6 locations), with only the estimates of the populations served being different. In other cases there may be some common locations and some that differ (e.g., with N=3), in which case the social planner would make a subjective decision on the locations to select.

In addition, when it is not possible to specify the coverage assumption, a robust approach can be applied by creating a model that combines aspects of the different models into one model or by using a minmax regret evaluation of the solutions found by the different models as shown previously. Similarly, if there is uncertainty about parameter values then the model can be run for different parameter values, either separately or in a combined manner, in order to find a robust solution. For example, the first and second radius of model 2 can be assumed to be 4km and 6km in one model run and 5km and 8km in a second model run or have both parameter sets incorporated into one robust model. Moreover, in the robust formulation for addressing demand uncertainty, if the total demand is unchanged and the deviation percentage in each village is the same, the optimal solution of the nominal problem is the same as that of the robust problem.

In summary, outreach is a critical component of EPI vaccination programs in low and middle income countries. However, there are no standard guidelines for outreach and these activities tend to be conducted in a fairly *ad hoc* fashion. In particular, the problem modeled in this paper is motivated by vaccination activities in India, and our approach is based on adapting facility location models to the outreach coverage problem. Based on past and ongoing work

related to vaccine logistics that we have done with a number of countries in Asia and sub-Saharan Africa, we feel that these models can aid decision makers when they are establishing outreach policies. The resulting outreach plan affects the performance of the entire vaccine supply chain because the demand for vaccines at all levels of the supply chain will vary with the outreach plan and the resulting vaccine coverage.

3.0 MODULAR VACCINE PACKAGING TO INCREASE PACKING EFFICIENCY

3.1 INTRODUCTION

Currently, individual vaccines vials and their component packaging vary significantly in overall length, width, and height. This is because the vaccine packaging size is determined by the dimensions of both individual cylindrical vials (each containing one or more doses of vaccine) and rectangular inner packs that typically contain 10, 20, 50 or 100 vials of a particular vaccine. The variability of inner pack and vial dimensions may hinder efficient vaccine distribution because it constrains packing of cold boxes and vaccine carriers to quantities that are often inappropriate or suboptimal in the context of country-specific vaccination guidelines. In particular, estimating storage space requirements is more difficult with non-standard sizes and in a resource constrained system it may not be possible to take all the vaccines needed in a carrier because of the inefficient packaging.

Modularized packaging is one way to address this because the consequent increase in packing efficiency has the potential to reduce storage space requirements and replenishment frequencies. The standardization of packaging also has the benefit of making operations much simpler for personnel since vaccines can be more easily packed and space requirements can be more easily estimated. While vaccine vial size has been a recent topic of academic and policymaker interest, explorations of alternative packing configurations have not yet addressed

inner packs (Assi, et al., 2011; Dhamodharan & Proano, 2012; Parmar, Baruwa, Zuber, & Kone, 2010; Lee, et al., 2011; Lee & Burke, 2010; Assi, et al., 2013; Brown, et al., 2014; Drain, Nelson, & Lloyd, 2003). The packing analysis in this paper proposes that a solution to inefficient packing caused by inner pack and vial size variability is a modular packaging system (where vial and inner pack dimensions are more consistent between different vaccines) that allows for more effective packing into cold boxes and vaccine carriers.

3.2 METHODS

We developed in Microsoft Excel (Microsoft Corp.) a spreadsheet model that evaluated the impact of different packing schemes for the Benin routine regimen plus the introduction of the Rotarix vaccine. The Benin routine vaccine regimen includes Bacillus Calmette-Guerin (BCG), Tetanus, Measles, Oral Polio, Yellow Fever, Diphtheria-Tetanus-Pertussis-Hepatitis B-Haemophilus influenzae type B (DTC-HepB-Hib), Pneumococcal Conjugate (PCV13), and Rotavirus (Rota) vaccines. Specifically, the model is used to compare the current packing scheme to that of a proposed modular packaging system.

The storage device considered is the Dometic RCW25, which is prequalified by the WHO, is used in over 100 countries and was noted as a commonly used storage device in a recent study of in-country vaccine transport devices (PATH & World Health Organization, 2013; World Health Organization, 2010). The RCW 25 has a vaccine storage volume with length 40.5 cm, width 26.5 cm and height 19 cm after it is packed with conditioned ice. In Benin, workers at a “Health Post” (the lowest level of the vaccine distribution chain where vaccines are administered) typically travel to a “Commune Store” once per month to pick up vaccines; the amount of vaccines picked up depends on the population characteristics of the catchment area

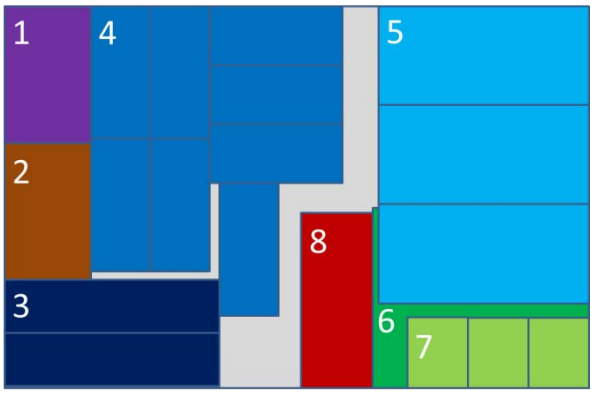
served by the Health Post and is determined by workers at the Health Post based on prior months' demand. The vaccines are transported back to the Health Post in a vaccine carrier using a motorcycle. In determining packing efficiency, analyses of both current inner pack/vial sizes and the proposed modular system considered the number of fully immunized children (FIC) possible and packing efficiency (% space occupied) per fully packed device. The FIC metric ensures that our evaluations are with vaccine carriers that transport the suite of vaccines required for an FIC (as opposed to simply filling the carrier with just one or two types of vaccines).

3.2.1 Conventional packaging configuration

The dimensions in Table 7 were used for analyses of existing, conventional inner packs and their constituent vials; the volume of the inner pack is simply the product of its length, width, and height as described by the vaccine manufacturer. These dimensions were used to determine the number of conventional inner packs for each vaccine type that could be placed in the RCW25 in order to maximize the FIC per device. To pack the device, we used manual modifications. Note that each inner pack could be positioned in any orientation and that inner packs of the same type could have multiple orientations. For each inner pack combination we placed the inner packs into the storage device until its dimensions prohibited the addition of any more.

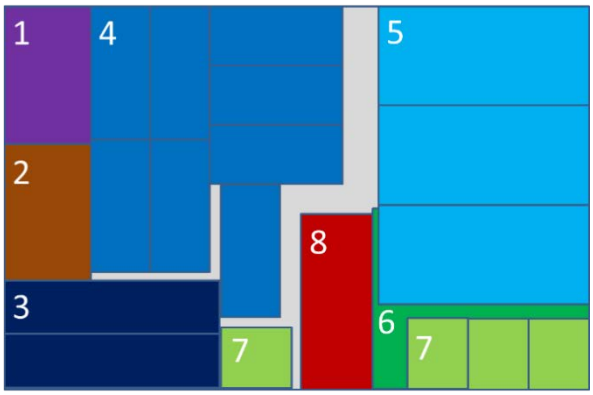
Table 7. Conventional inner pack dimensions

Vaccine Type	BCG	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib liquid	PCV13	Rota
Length (cm)	18.5	10.6	18.5	15	10.6	18	17.9	14.6
Width (cm)	9.5	4.7	9.5	12.5	4.7	14.9	9.2	8.5
Height (cm)	6	5.1	6	7.5	5.1	3.7	4.1	6.9
volume(L)	1.05	0.25	1.05	1.41	0.25	0.99	0.68	0.86
Vials/inner pack	50	10	50	100	10	100	50	50



1	BCG	1 pack 1 layer; 18.5 cm height
2	Measles	1 pack 1 layer; 18.5 cm height
3	DTC-HepB-Hib	2 packs 1 layer; 18 cm height
4	PCV13	8 packs 1 layer; 17.9 cm height
5	Rota	5 packs 2 layers; 2×8.5 cm height
6	Oral Polio	1 pack 1 layer; 7.5 cm height
7	Tetanus	3 packs 1 layer; 10.6 cm height
8	Yellow Fever	3 packs 3 layers; 3×4.7 cm height

Figure 7. Packing arrangement in RCW25 for conventional inner packs (Top view)



1	BCG	1 pack 1 layer; 18.5 cm height
2	Measles	1 pack 1 layer; 18.5 cm height
3	DTC-HepB-Hib	2 packs 1 layer; 18 cm height
4	PCV13	8 packs 1 layer; 17.9 cm height
5	Rota	5 packs 2 layers; 2×8.5 cm height
6	Oral Polio	1 pack 1 layer; 7.5 cm height
7	Tetanus	4 packs 1 layer; 10.6 cm height
8	Yellow Fever	4 packs 4 layers; 3×4.7 cm height

Figure 8. Packing arrangement in RCW25 for conventional inner packs with two additional inner packs

In our simulation of storage device packing, the device is filled with the objective of maximizing the number of children that could be fully immunized as per the Benin routine vaccination schedule. This involved two steps. In Step 1 we considered the vaccine schedule required for each FIC – for each vaccine we determined the average number of children that can be fully vaccinated per inner pack, based on the scheduled number of doses, the wastage rate, the number of doses per vial and the number of vials per inner pack, as described in Table 8. For example, for BCG the vaccine schedule is one dose per child and the wastage rate is 50%;

therefore, on average, 1/(1-.50) = 2 doses are needed per FIC (note that in the remainder of this chapter when we reference FIC we mean the *expected* FIC given the average wastage rates given in Table 8) . BCG has 20 doses per vial and an inner pack of BCG contains 50 vials, therefore the inner pack contains 50*20 = 1,000 doses total. Because 2 doses on average are needed per FIC, on average 1,000/2 = 500 children can be immunized per inner pack of BCG.

Table 8. FIC calculations per inner pack

	BCG	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib liquid	PCV13	Rota
Scheduled doses per child	1	2	1	4	1	3	3	2
Wastage rate	0.5	0.15	0.45	0.17	0.45	0.05	0.01	0.01
Doses per vial	20	10	10	20	10	2	1	1
Vials per inner pack	50	10	50	100	10	100	50	50
FIC per inner pack	**500**	**42.5**	**275**	**415**	**55**	**63.33**	**16.5**	**24.75**

In Step 2, beginning with one inner pack of each vaccine type, we incrementally increased the number of inner packs in order to increase the expected number of FIC that can be served, as illustrated in Table 3-3. Initially we place one inner pack of each vaccine type into the carrier, resulting in the FIC values given in the first row (“One of each”). The expected number of FIC that the carrier can serve is the minimum FIC value in the row, which is 16.5 for PCV13 (bold, highlighted); therefore, we next add an inner pack of PCV13 so that there is enough PCV13 to vaccinate 2 * 16.5 = 33 children. This results in the FIC values given in row 2 (“+1 PCV13”), with a new limiting FIC value of 24.75 determined by Rotarix; therefore we next add an inner pack of Rotarix. This process is repeated until there is no more room in the storage device. This results in the inner pack values shown in the last row (“FINAL”), with a final FIC value of 123.75.

Table 9. Packing current inner packs into the device

		BCG	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib liquid	PCV13	Rotarix
One of Each	Number of inner packs	1	1	1	1	1	1	1	1
	FIC	500	42.5	275	415	55	63.33	**16.5**	24.75
+1 PCV13	Number of inner packs	1	1	1	1	1	1	2	1
	FIC	500	42.5	275	415	55	63.33	33	**24.75**
+1 Rotarix	Number of inner packs	1	1	1	1	1	1	2	2
	FIC	500	42.5	275	415	55	63.33	**33**	49.5
FINAL	Number of inner packs	1	3	1	1	3	2	8	5
	FIC	500	127.5	275	415	165	126.67	132	**123.75**

In determining the exact inner pack configuration within the storage device our approach was slightly different for conventional and modular inner packs. The conventional inner packs are all of different sizes and their packing was therefore done by trial and error filling from the bottom of the storage device. It should be noted that an optimization approach such as 3-dimensional bin packing would be computationally intensive and unrealistic in the field; rather we tried to replicate what a typical field worker might do in an effort to choose among realistic solutions. While the packing is easy in the early stages, as the number of inner packs increases (at each step in Table 3-3) it becomes more difficult as we need to abandon the current configuration and start afresh. We were able to pack the number of inner packs shown in the last row of Table 9 using the configuration shown in Figure 7.

3.2.2 Proposed modular packaging configuration

In designing modular packaging we assumed that all vaccines have vials with the same diameter but that the vial heights can change to account for differences in dose volumes. This provided uniform vial size in two dimensions and variation in only one dimension. Our data sources provided the rectangular dimensions of existing conventional inner packs but not the cylindrical dimensions of individual vials. We computed these by dividing the length or width of the inner pack by the number of vials in the length or width dimension. When there was inconsistency in the unit length and the unit width, we choose the larger value to be conservative. These values were then used to determine current vaccine vial volume, in order to design similar modular vials.

Specifically, to determine the ideal modular vaccine vial diameter, we analyzed the effects of multiple potential vial diameter sizes on packing efficiency. There are four main considerations for deciding the ideal modular vaccine vial diameter:

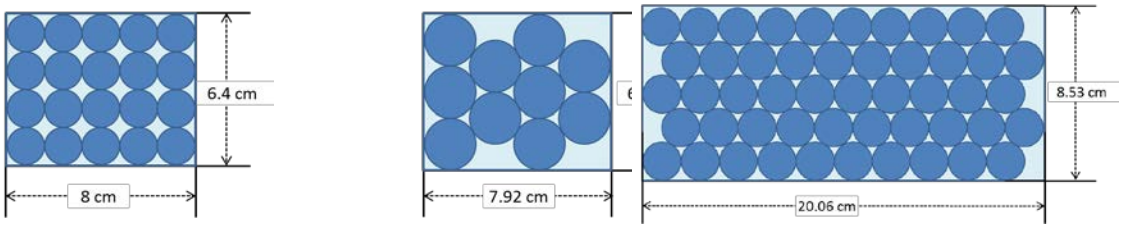
1) The number of vials in an inner pack: We required the quantities per inner pack to be values that are easy for counting, such as 10, 20, or 50.
2) Area efficiency: The modular vaccine vial diameter needed to result in an inner pack configuration that would fit well into the space available in the storage device.
3) Vial size as it relates to dose volume: The goal was to create standardized vial sizes but also make them similar in size to conventional vials to preserve existing dose per vial calculations – thus we found candidate vial diameters by calculating the area occupied by the vials when using 10, 20, and 50 vials in an inner pack.
4) Packing array: We considered diameters that could work with both hexagonal and rectangular packing within rectangular inner packs.

The above analysis yielded three potential diameters of 1.6 cm, 2.2 cm, and 1.91cm. For each diameter and each vaccine type, we calculated the modular vial height based on the volume of the original, conventional vial; the calculated modular vial heights are shown in Table 10, and also determine the height of the inner pack in which the vials are subsequently stored. The 1.6cm diameter vials require relatively large heights while the 2.2 cm diameter vials require relatively small heights, in order to maintain current volumes/doses per vial. Therefore, we also evaluated a modular system that uses a mixture of 1.6 cm diameter vials for some (small-volume) vaccines and 2.2 cm diameter vials for other (large-volume) vaccines. We also considered an intermediate vial diameter of 1.91 cm by itself.

We next examined the three different vial sizes in the context of potential inner pack dimensions; optimum inner pack dimensions are shown in Table 10, while the vial configuration within each inner pack and the corresponding dimensions are shown in Figure 9. Note that the inner packs for 1.6 cm diameter vials and 2.2 cm diameter vials are very similar in length and width; this was done purposely in order to maximize the efficiency of the fourth modular system that uses a combination of the two vial sizes. All three inner pack sizes were chosen such that they can be packed efficiently into the volume of the RCW25. From Table 10, for the 1.6 cm and 2.2 cm diameter vials, inner pack dimensions are approximately 8 cm long and 6.5 cm wide. Therefore, they can be stored 5-long along the 40 cm length of the storage device and 4-wide along the 26.5 cm width of the storage device. The result is that there are 20 stacks of inner packs, each occupying the same area, which can each be up to 19 cm tall. For the 1.91 cm diameter inner packs, there are 6 stacks of inner packs that can each be up to 19 cm tall. The different packing configurations for each vial size within the two dimensions (length × width) of the storage device are shown in Figure 10.

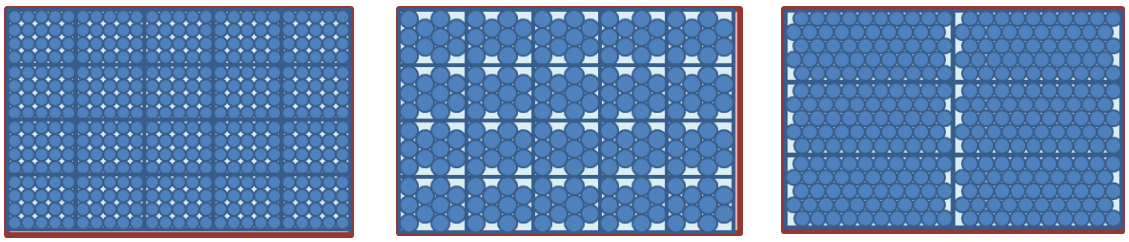
Table 10. Potential modular inner pack dimensions for different vial diameters

Diameter (cm)		BCG	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib liquid	PCV13	Rota
1.6	Length(cm)	8.00	8.00	8.00	8.00	8.00	8.00	8.00	8.00
	Width(cm)	6.40	6.40	6.40	6.40	6.40	6.40	6.40	6.40
	Height(cm)	8.24	9.95	8.24	5.54	9.95	3.91	5.28	6.73
2.2	Length(cm)	7.92	7.92	7.92	7.92	7.92	7.92	7.92	7.92
	Width(cm)	6.60	6.60	6.60	6.60	6.60	6.60	6.60	6.60
	Height(cm)	4.36	5.26	4.36	2.93	5.26	2.07	2.79	3.56
1.91	Length(cm)	8.53	8.53	8.53	8.53	8.53	8.53	8.53	8.53
	Width(cm)	20.06	20.06	20.06	20.06	20.06	20.06	20.06	20.06
	Height(cm)	5.78	6.98	5.78	3.89	6.98	2.74	3.70	4.72
1.6 + 2.2	Length(cm)	7.92	7.92	7.92	8.00	7.92	8.00	8.00	7.92
	Width(cm)	6.60	6.60	6.60	6.40	6.60	6.40	6.40	6.60
	Height(cm)	4.36	5.26	4.36	5.54	5.26	3.91	5.28	3.56
	Diameter(cm)	2.2	2.2	2.2	1.6	2.2	1.6	1.6	2.2



1.6cm diameter vials 2.2cm diameter vials 1.91cm diameter vials

Figure 9. Packing configurations within inner packs for each proposed modular vial size



1.6cm diameter 4x5 inner packs 2.2cm diameter 4x5 inner packs 1.91cm diameter 3x2 inner packs

Figure 10. Packing configurations within storage device

As opposed to the trial-and-error approach with the conventional inner packs as described in Section 3.2.1, we used a heuristic algorithm for packing the modular inner packs into the storage device. We experimented with two versions of the heuristics based on how field workers might fill the storage device. In version 1 the device was packed by starting on one side of the storage device and sequentially stacking inner packs vertically and building up multiple stacks (we refer to this as the *tower method*), while in version 2 we sequentially fill the storage device horizontally filling the storage device from the bottom and building up multiple layers (we refer to this as the *layer method*).

For both methods we started by assigning the storage orientations for inner packs as described in the previous paragraph, and then sorted inner packs in decreasing order of height. In the *tower* method we used a first-fit-decreasing heuristic where inner packs were stacked in decreasing order of height in a single tower until no more can be placed in that tower, and we then search for the largest inner pack that fits in the remaining space (Figure 11). When no inner packs can be fitted into the current tower a new tower is started and this procedure is repeated until all inner packs are exhausted. In the *layer* method, the inner packs are sequentially placed in the same layer in decreasing order of height until there is no more space in the layer to form several different towers. These towers are then built up layer by layer in a sequential fashion until all inner packs are exhausted (Figure 12).

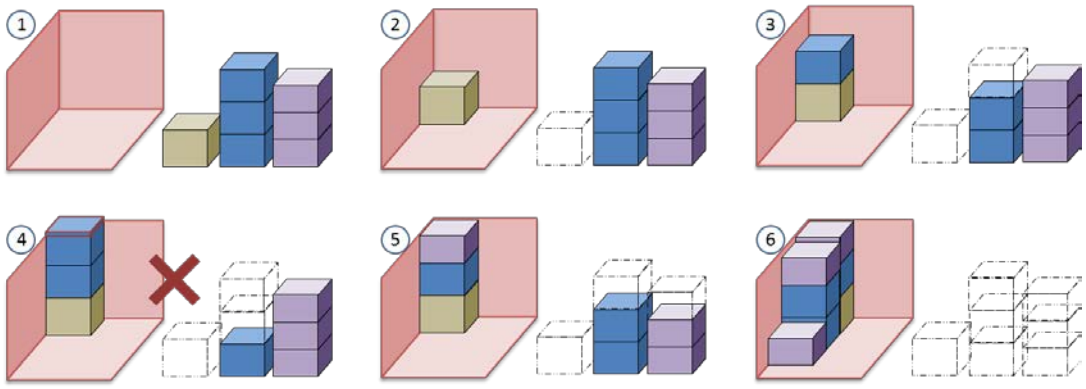


Figure 11. Tower packing method

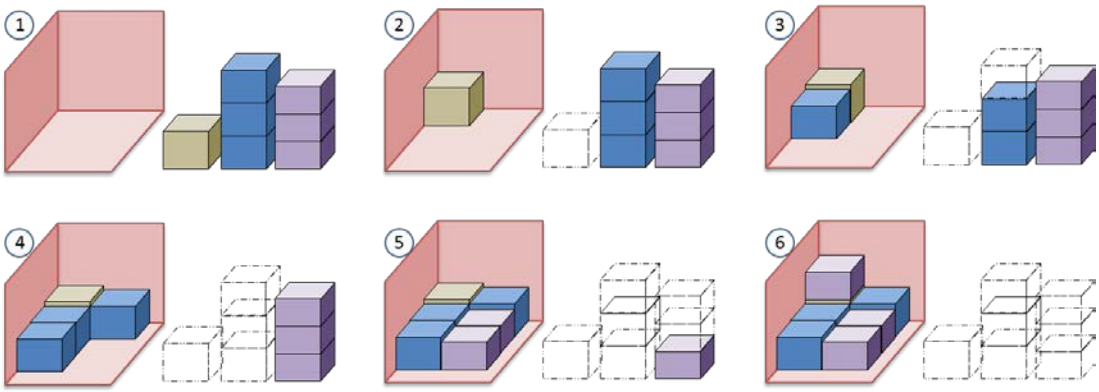


Figure 12. Layer packing method

In addition to the heuristic tower and layer methods, we also considered a mathematically optimized tower method (termed the *optimized method*) using the following model.

Notation

x_{ij}: Number of inner packs of vaccine i in the j^{th} tower

F: Number of fully immunized child who can be covered

c_i: Number of people who can be covered by one inner pack of vaccine i

f_i: Number of people who must be administrated vaccine i

h_i: Inner pack height of vaccine i

h: Storage device height

m: Number of towers in one storage device

n: Number of the vaccine types

$$Max \quad F \tag{45}$$

subject to

$$c_i \sum_{j=1}^{m} x_{ij} \geq F \quad \text{for } i = 1 \text{ to } n \tag{46}$$

$$\sum_{i=1}^{n} h_i \, x_{ij} \leq h \quad \text{for } j = 1 \text{ to } m \tag{47}$$

$$x_{ij} = \{0, 1, 2, \dots\} \tag{48}$$

The objective (45) is to maximize the number of fully immunized children F that can be covered by the combination of inner packs of each vaccine in one storage device. Constraint (46) insures that the number of FIC cannot exceed the number of people who can be administrated each vaccine type. Constraint (47) insures that the sum of height of the inner packs in each tower must be less than the height of the storage device. Constraint (48) insures that we only use integral numbers of inner packs (no partial inner packs are allowed.) This model determines the optimal way to combine the inner packs into towers to attain the maximum possible FIC value. This linear integer programming model is presented mainly as a point of reference for bounding the performance of our heuristic approach, since it is unrealistic to expect that this approach will be used in the field.

3.3 RESULTS

3.3.1 Conventional packing efficiency

The number of children who can be fully vaccinated with each vaccine type for the conventional inner packs is shown in the bottom row of Table 9 and the maximum expected FIC served by a single storage device is 123. The resulting configuration of inner packs within the device is illustrated in Figure 7.

Currently, the FIC-optimizing configuration of conventional inner packs occupies 16.71 liters, representing 81.93% of the available volume of the RCW25; we refer to this as the volume efficiency of the packing. Although there is not enough empty space to add an inner pack of the vaccine currently determining the maximum FIC value (Rotarix), we can still use this space for other vaccines if we wish to do so. Thus, after filling the device to its FIC capacity, it is possible to add in two inner packs of Yellow Fever or two inner packs of Tetanus or one inner pack of each (the inner packs of these two vaccines are the same size). The occupied volume and volume efficiency now rise to 17.22 liters and 84.4% respectively. Figure 8 illustrates the arrangement with one extra inner pack of yellow fever (on top of the previous three) and one extra inner pack of tetanus (stored vertically in the empty space shown in Figure 7).

It is important to note that these packing efficiencies were achieved by evaluating many different possibilities and therefore almost certainly reflect a higher packing density than would be achieved in practice, since storage devices are generally not packed and repacked multiple times. Thus, it is not likely that this high a degree of space utilization is regularly achieved in actual practice

3.3.2 Conventional versus modular packing efficiency

The maximum FIC that can be served by one RCW25 given the current inner pack sizes is 123 as calculated above; the same methodology can be applied using the modular inner pack data and the results are shown in Table 11 (detailed information about the numbers of doses and inner packs achieved with conventional packing and each modular packaging system can be found in Table 12). The results also show that the tower method often outperforms the layer method and the optimized method always performs as well as or better than the layer and tower methods in terms of vaccine storage. In the discussion below we use the term "baseline" or "base" to refer to the 123 FIC obtained with conventional packaging.

Table 11. Maximum FIC and occupied volume for different proposed modular vaccine vial diameters

Diameter (cm)	Layer Method		Tower Method		Optimization Method	
	FIC	Vol. %	FIC	Vol. %	FIC	Vol. %
2.2 (10 vials)	152 (96.2%)	92.6%	155 (98.1%)	94.1%	158 (100%)	94.8%
1.6 (20 vials)	138 (87.3%)	81.3%	148 (93.7%)	86.6%	158 (100%)	90.6%
1.9 (50 vials)	148 (100%)	87.9%	148 (100%)	87.9%	148 (100%)	87.9%
Mix 1.6+2.2	148 (93.7%)	87.4%	145 (91.8%)	86.1%	158 (100%)	91.5%

Note that the numbers below the FIC in the parentheses is the percentage

Generally speaking, all modular packing systems exceed baseline packing efficiency, both in terms of maximum FIC served and volume efficiency. For example, using modular inner packs with vial diameter 2.2 cm, 155 FIC can be served per storage device, with a 94.1% volume efficiency, when the tower method is applied. It is also worth noting that (a) this increase in

efficiency is mainly because of the new inner pack sizing and is not dependent on the specific approach used to store the inner packs within the device, and (b) potential improvements are likely to be even higher because any optimization of conventional packing in the field is highly unlikely and in reality the actual FIC figure attained is likely to be much lower that our baseline value of 123, which was obtained after significant effort. For catchment areas with higher populations where larger volumes of vaccine are required, this has the potential for reductions in the number of vaccine carriers required and/or reductions in the replenishment frequency, which in turn could yield lower transportation and personnel costs. Estimating such potential savings would be the next step in analysis of this novel modular packaging system.

Table 12. Total doses, inner packs, and FIC by antigen for conventional versus proposed modular packaging configurations within the Dometic RCW25

	BCG		**Tetanus**		**Measles**		**Oral Polio**		**Yellow Fever**		**DTP-HepB-Hib**		**PCV13**		**Rota**		
	Total Doses	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	*Total Doses*	*Inner Packs*	***FIC***
Conventional Packaging Configuration	1000	1	300	3	500	1	2000	1	300	3	400	2	400	8	250	5	**123**
Proposed Modular Packaging Configuration																	
2.2 cm Vial Diameter																	
Layer Method	400	2	400	4	300	3	800	4	300	3	480	24	470	47	310	31	**152**
Tower Method	400	2	400	4	300	3	800	4	300	3	500	25	470	47	320	32	**155**
Tower Opt. Method	400	2	400	4	300	3	800	4	300	3	500	25	480	48	320	32	**158**
1.6 cm Vial Diameter																	
Layer Method	400	1	400	2	400	2	800	2	400	2	440	11	420	21	280	14	**138**
Tower Method	400	1	400	2	400	2	800	2	400	2	480	12	460	23	300	15	**148**
Tower Opt. Method	400	1	400	2	400	2	800	2	400	2	520	13	480	24	320	16	**158**
1.9 cm Vial Diameter																	
Layer Method	1000	1	500	1	500	1	1000	1	500	1	500	5	450	9	300	6	**148**
Tower Method	1000	1	500	1	500	1	1000	1	500	1	500	5	450	9	300	6	**148**
Tower Opt. Method	1000	1	500	1	500	1	1000	1	500	1	500	5	450	9	300	6	**148**
1.6 + 2.2 cm Vial Dia.																	
Layer Method	400	2	400	4	300	3	800	2	300	3	480	12	460	23	300	30	**148**
Tower Method	400	2	400	4	300	3	800	2	300	3	480	12	440	22	300	30	**145**
Tower Opt. Method	400	2	400	4	300	3	800	2	300	3	520	13	480	24	320	32	**158**

3.4 ANALYSIS WITH MORE STORAGE DEVICES

Even though the RCW 25 is a widely used cold box, many other devices are used in practice and the modular packaging which is designed for the RCW 25 could be used with other storage devices. The question of interest is, if this occurs, does this modular packaging still work better than conventional packaging? In order to answer this, the space efficiency of the modular packaging system is examined using the same analysis method used in the previous research by evaluating the modular packaging configurations for the RCW 25 when they are applied to another storage device.

3.4.1 Selection of the new device

First, we consider the storage devices found in the WHO's pre-qualified storage device list that have similar volumes to that of the RCW 25. These devices are shown in Table 13.

Table 13. WHO pre-qualified storage device list

PQS code	Model	Length(cm)	Width(cm)	Height(cm)	Volume(liter)
E004/025	CB-20-CF	53	23	20	24.4
E004/031	AICB 503 L	45.5	31	16	22.6
E004/015	ACB 503L	45.5	30.5	16	22.2
E004/024	ACB 316 L	44.2	29.3	18.3	23.7
E004/014	ACB 444 L	45	29.4	16.4	21.7
E004/013	RCB 444 L 23	45	30	17	23.0
E004/010	AICB 444 L	44.8	30	16.7	22.4
E004/036	RCB 444L-A	45	30	15	20.3

Seven of the storage devices have dimensions of about 45 cm in length and 30 cm in width. Since the volume of the RCW 25 is 20.3 liters, the RCB 444L-A which has 20.3 liters volume is chosen to analyze the space efficiency of the modular packaging system.

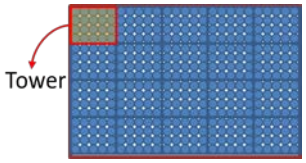
3.4.2 Results for the new device with the inner pack configurations for the RCW 25

When the original inner pack sizes are used, the RCB 444L-A can store vaccines that are able to cover 126.6 FICs. Note that this packing configuration was found by evaluating numerous configurations and represents a packing density that would be difficult to achieve in practice. Table 14 shows the number of FICs when the modular inner packs which were created for the RCW 25 are used to fill the RCB 444L-A. When 1.6 cm diameter vials are used, a maximum of 21 (3 × 7) tower are available in the RCB 444L-A. For 2.2 diameter vials, a maximum of 20 (4×5) tower are available. When the inner packs are stored vertically in the tower, 112.2 FICs can be covered when using 1.6 cm diameter vial inner pack with the tower method, and 118.8 FICs for 2.2 cm diameters with the layer method. Since the inner pack dimensions are not designed for the RCB 444L-A, after filling up the tower in the storage device, there are spare spaces where additional inner packs can be stored. If the spare space is used to store vaccines, the FICs for the 1.6 and 2.2 diameter vial inner packs increase to 145 with the layer method and 152 with the tower method each.

Table 14. FIC for the heuristic and optimizing methods

Proposed Modular Packaging Configuration	No. of tower[1)]	Tower method		Layer method		Optimizing method	
		In towers[2)]	+ Spare space[3)]	In towers[2)]	+ Spare space[3)]	In tower[2)]	+ Spare space[3)]
1.6 cm diameter	21	112.2 (100%)[4)]	138.6 (87.4%)	110.0 (98%)	145.2 (91.6%)	112.2	158.6
2.2 cm diameter	20	118.8 (97.3%)	152.0 (98%)	112.2 (91.9%)	145.7 (93.9%)	122.1	155.1
1.91 cm diameter	6	99.0 (100%)	126.6 (85.2%)	99.0 (100%)	126.6 (85.2%)	99.0	148.5
1.6 cm +2.2 cm mixed	20	114.0 (96%)	151.8 (100%)	110.0 (92.6%)	138.6 (91.3%)	118.8	151.8

1) The footprint of a tower is the area that one modular inner pack takes in the storage device.



2) When vaccines are filled only in towers
3) When vaccines are filled in towers and any empty space after filling the towers
4) Percentage ratio of the FIC of the tower/layer method to the optimizing method

When the inner packs are stored only in towers, the number of FIC is less than 126.6. However, when we consider that 126.6 is not the number of FIC that we can expect to attain in practice, the value that we obtain with only tower packing is reasonably good. In addition, because the spare space can be utilized to store more inner packs, the modular packing systems exceed the baseline packing efficiency. Clearly, the optimizing method provides better results than the two heuristic methods, but the FIC difference between the heuristic methods and the optimizing method is relatively small so the heuristic methods can be used to fill the storage devices almost as well as the optimizing method does.

3.4.3 New configuration for the RCW 25 and the new device

Now, we consider new modular configurations that consider the size of the RCW 25 and the new device. These configurations allow more modular inner packs to be stored than the modular configurations designed for only the RCW 25. Using the same methods as in section 3.2.2, the proper inner pack dimensions are chosen and shown in table 15.

Table 15. New modular packaging configuration for RCW 25 and RCB 444L-A

New Modular Packaging Configuration	BCG-20	TT	Mea	TOPV	YF	DTP-HepB	PCV13	RV
1.76 (20 vials per pkg)	8.8 7.04 6.81	8.8 7.04 8.22	8.8 7.04 6.81	8.8 7.04 4.58	8.8 7.04 8.22	8.8 7.04 3.23	8.8 7.04 4.36	8.8 7.04 5.56
2.45 (10 vials per pkg)	8.82 7.35 3.51	8.82 7.35 4.24	8.82 7.35 3.51	8.82 7.35 2.36	8.82 7.35 4.24	8.82 7.35 1.67	8.82 7.35 2.25	8.82 7.35 2.87
1.5 (20 vials per pkg)	7.5 6 9.38	7.5 6 11.32	7.5 6 9.38	7.5 6 6.30	7.5 6 11.32	7.5 6 4.45	7.5 6 6.00	7.5 6 7.66
2.08 (10 vials per pkg)	7.488 6.24 4.88	7.488 6.24 5.89	7.488 6.24 4.88	7.488 6.24 3.28	7.488 6.24 5.89	7.488 6.24 2.31	7.488 6.24 3.12	7.488 6.24 3.98
2.14 (50 vials per pkg)	22.47 9.55 4.61	22.47 9.55 5.56	22.47 9.55 4.61	22.47 9.55 3.10	22.47 9.55 5.56	22.47 9.55 2.19	22.47 9.55 2.95	22.47 9.55 3.76

Table 16 shows the number of the towers for each device for different vial diameters. The 1.76 cm and 2.45 diameter vial inner packs have a similar width and length, so they can be used interchangeably. The 1.5 cm and 2.08 diameter vial inner packs also have a similar width and length and can be used interchangeably, but only 28 towers in the RCW 444L-A are available when they are used interchangeably.

Table 16. The number of the towers for RCW 25 and RCB 444L-A

New Modular Packaging Configuration	RCW 25	RCB 444L-A
1.76 (20 vials per pkg)	15 towers (3 × 5)	20 towers (4 × 5)
2.45 cm (10 vials per pkg)	15 towers (3 × 5)	20 towers (4 × 5)
1.5 cm (20 vials per pkg)	20 towers (4 × 5)	30 towers (5 × 6)
2.45 (10 vials per pkg)	20 towers (4 × 5)	28 towers (4 × 7)
2.14 cm (50 vials per pkg)	4 towers (2 × 2)	6 towers (2 × 3)

However, note that these new configurations might not be realistic because the heights of some vials are too short to hold vaccine. Vials less than 3 cm in height may not be tall enough to hold vaccine. The short vials occur because the vial size change only considers total vial volume and ignores the vial shape. For example, DTP-HepB inner packs with diameter 2.45 cm have a height of 1.67 cm, which is definitely too short.

3.4.4 Results with new configurations

Table 17 shows the number of FICs for each device when only towers are used for packing. In most cases, a modular packaging system can hold more vaccines, as measure by FIC, than the conventional packaging configuration (123.6 for the RCW 25 and 126.6 for the RCB 444L-A). Note that we do not consider filling any additional spare space so as to simplify the packing analysis. Using the spare space permits a storage device to hold more vaccine but makes the packing procedure more complicated because a health worker has to consider many different ways to utilize the spare space. In addition, even without utilizing the spare space, the modular packaging results in better filling of the storage devices than conventional packaging.

Table 17. FIC for RCW 25 and RCB 444L-A with new configurations

New Modular Packaging Configuration	RCW 25			RCB 444L-A		
	Tower	Layer	Optimizing	Tower	Layer	Optimizing
1.76 cm	138.6 (99.5%)[1)]	132 (94.6%)	139.3	132 (88.9%)	138 (92.9%)	148.5
2.45 cm	143.6 (98.6%)	138.6 (95.1%)	145.7	143.6 (92.6%)	145.2 (93.6%)	155.1
1.5 cm	132 (100%)	118.8 (90.0%)	132	151.8 (92.2%)	151.8 (92.2%)	164.7
2.08 cm	138.6 (100%)	135.3 (97.6%)	138.6	141.9 (93.5%)	145.2 (95.7%)	151.8
2.14 cm	115.5 (93.3%)	123.8 (100%)	123.8	148.5 (100%)	148.5 (100%)	148.5

1) Percentage ratio of the FIC of the tower/layer method to the optimizing method

Obviously, the FIC for the RCW 25 decreases and the FIC for the RCB 444L-A increases. When the vial configurations for the RCW 25 are used and only the tower space is used, the maximum FICs for each device are 158.0 and 122.1, respectively. However, when the new configurations for both devices are used and only the tower space is used, the maximum FICs for each device are 145.7 and 155.1, respectively. This implies that the new packaging configuration results in greater vaccine storage if equal numbers of the two devices are used.

3.5 DISCUSSION AND CONCLUSIONS

The results of this study show that modular inner packs permit more vaccines to be stored in the storage device. This follows from the fact that we choose to standardize vial diameters and inner pack sizes, which in turn leads to easier and more efficient packing in a vaccine carrier. Under the current situation with widely varying inner pack sizes it is not possible to arrive at a consistent and space-efficient packing arrangement. Additionally, the modular inner packs would actually provide even greater packing efficiency because the height of the inner packs was

determined conservatively in our analysis; adjusting for this will likely increase the packing efficiency difference by approximately an additional 5%. We also recommend the tower approach over the layer approach since the former generally provides slightly better packing efficiency. The mathematical model allows more vaccine to be stored in the storage device, but the heuristic methods also provide good packing efficiency in all examples. Therefore, if the optimizing method is not available, the heuristic ones can provide a good packaging solution. Finally, the optimized tower approach would be unrealistic in practice and its results serve mainly to provide an upper bound on performance. Table 11 shows that the heuristic methods do well in relation to this bound.

Since different shapes and sizes of storage devices are used in practice, it is impossible to design a modular packaging scheme that fits all storage devices precisely. However, if there is a commonly used storage device in a country and it is possible for the vaccine manufacturers to manipulate the size of the modular packaging, then selecting the right dimension that give a precise fit for the device would be a good strategy to employ. Even if there are different storage devices in a country, as long as a modular packaging system is utilized, more vaccines can be packed than when conventional packaging is used. We also accrue additional benefits from using modular packaging including simple, consistent and fast packing, ease of counting the number of vials, and easier handling in general.

It should be noted that if the demand is not high enough to warrant filling the cold box (e.g., at a catchment area with a low population) then packaging is obviously less of an issue. Simply filling the carrier with additional vaccines to maximize FIC might not be appropriate if there is potential for wastage of excess vaccines at such locations. The issue of packaging is of greater importance when we have sufficient demand and the cold boxes we have cannot take

everything needed because of the inconsistent packaging sizes, or when inconsistent sizes make it difficult for health care workers to manage limited space in a simple and efficient fashion.

In summary, there are several advantages to using the modular packaging as listed below; the first two are probably the most important.

1. It achieves higher packing densities for a reasonable packing method such as the tower or the layer approach, as indicated by the data in Table 3-5. Also, recall that the heights of the modular inner packs were found by using conservative volume estimates and therefore the actual packing density differences between conventional and modular systems will likely be a few percentage points greater. It is also important to note that the conventional packing densities discussed assume that packers optimize space efficiency by packing and re-packing to achieve maximum efficiency. Thus, the packing densities achieved in practice are probably lower, which further increases the advantage of using the modular systems.
2. The modular packing procedure is much simpler and more consistent. Vaccines are simply stacked vertically in the twenty or six vertical stacks (depending on the vial size); there is no need to explore numerous complicated orientations and geometrical configurations. Thus, high packing efficiencies can be obtained consistently with little effort or special expertise required. This is a tremendous advantage from a practical standpoint because the personnel packing the storage devices will not require special training to ensure that carefully planned packing procedures are followed routinely in the field.
3. The simplified modular packing procedure will be faster since the person packing the storage device does not have to spend time exploring different configurations.

4. Counting the number of vials is easier because the inner packs have uniform quantities (this advantage is somewhat reduced if more than one standard size is adopted).
5. It is easier to handle the inner packs because they are all the same size, rather than trying to handle vaccines with different inner pack sizes. For example, transporting a stack of vaccines that has an inner pack that is 12cm × 15cm on top of an inner pack that is 15cm × 18cm which is on top of an inner pack that is 20cm × 20cm is more difficult to do without toppling it than a stack of three inner packs that all have the same dimensions.
6. Ideally, the vaccines should be packed with about 1cm of clearance space in between each inner pack to promote good air flow and uniform cooling (especially in refrigerators). If the inner packs have a consistent modular size, this would facilitate inserting spacers in between the stacks of inner packs to insure proper clearance is maintained.
7. If the inner packs are a consistent size, then cold storage devices can be manufactured with storage spaces that have dimensions that most efficiently accommodate the inner packs.

These benefits comes from the power of standardization. In this chapter, we have focused on standardization of vaccine packaging by changing packaging configurations. The modular packaging designed for a storage device can decrease wasted space in the storage device and can make it possible to utilize easy stacking methods. If the storage devices are also standardized along with the modular packaging size, the space efficiency could be maximized over an entire country.

While our analysis suggests that modular packaging systems offer benefits over conventional vaccine packaging in the form of increased potential FICs, higher packing

densities, and simplifying the process of a worker packing a storage device, there are several limitations to our study. First, we assumed a single conventional packaging type for each existing vaccine, while it is likely that existing packaging varies for vaccines from different manufacturers or with different dose schedules. Similarly, in designing a potential modular packaging system, we assumed that all vaccines could fit in new, optimized vials based on the volumes of vials currently in use. This may not be the case for all existing vaccines. Third, our packing approach is a heuristic algorithm related to inner pack heights and if these heights are widely different it might not provide packings that are as good as the ones in our illustration. Finally, in order to quantify the economic benefits of improved packaging, a potential next step would be to utilize a vaccine supply chain modeling software, such as HERMES(Assi, et al., 2011; Lee, et al., 2011; Assi, et al., 2013), to determine the economic impact of changing packaging sizes. The impact could vary significantly depending on the country and circumstances (e.g., vaccine regimen), and such an analysis would require extensive simulation experiments and could be the basis of a future study.

Our analysis suggests that modular packaging systems could offer significant advantages over conventional vaccine packaging systems with respect to space efficiency when combined with a reasonable packing method such as the layer or tower method, when they are stored in standard vaccine carrying devices. This allows for more vaccines to be stored within the same volume while also simplifying the procedures used by field workers for packing storage devices. Ultimately, this could be a simple way to help increase vaccine coverage worldwide.

4.0 APPLYING LEAN CONCEPTS TO MANAGE VACCINE INVENTORY

4.1 INTRODUCTION

Vaccines administered at clinics or health centers are typically supplied from an upper level distribution location. The replenishment of vaccines at a clinic usually happens at regularly scheduled intervals (e.g., once a month) and requires completing vaccine ordering processes such as determining how many vaccine doses remain and requesting the amounts necessary to cover the forecast demand before the next replenishment. This vaccine ordering process is executed by health workers at clinics across the country. It is complicated by the fact that there might be five to ten different vaccine types (e.g., measles, DTP, polio, etc.) and also that vaccines come in multi-dose vials where the number of doses in a vial is different for different vaccine types. In a typical clinic, the health worker counts and records the remaining vaccine vials and translates this into a number of doses. He then determines how many net doses would be required to meet the forecast demand until the next replenishment point and translates this into the number of vials needed for the next inventory cycle. This is done for each different vaccine and a combined order for vials is then placed with the higher level.

At the upper level distribution location another health worker counts the number of vials ordered by the clinic for each vaccine type and prepares them for delivery to or pickup by the clinic. The same distribution location will typically service a number of different clinics in a

similar fashion. The vaccines are then transported to the clinic. Currently, an individual vial is used as the ordering unit at the clinic, and since this is the smallest physical unit in the distribution chain, ordering in vials (as opposed to cases or standard packs of vials) does help to minimize clinic vaccine inventory. This is important because cold storage capacity for vaccines can often be quite limited at clinics. However, personnel at clinics who perform logistical activities are often poorly trained and lacking in the skills to effectively perform these activities. The steps in the replenishment process can be tedious and even trained workers can make mistakes in counting and recording the number of remaining vials of several different kinds of vaccines, and managing and replenishing inventory at the individual vial level requires significant effort. Moreover, Steele (2014) reports that immunization supply chain functions are frequently performed in developing countries by pharmacists, clinicians and drivers, as opposed to workers who are trained specifically on supply chain functions. She points out that vaccine supply chain practices are poor because of poor monitoring systems, resulting in poor data for demand forecasting and long procurement processes.

In this chapter, we conduct an ordering policy analysis with respect to the ordering unit, and based on this analysis we recommend the use of inner packs (the next larger packaging unit), rather than a vial, when ordering vaccines. In addition to simplifying the ordering process used by healthcare workers at the clinics, we show that it reduces the likelihood of vaccine stockouts and thus also improves overall vaccination levels at clinics by giving the patient more opportunities to get vaccinated. The basic idea behind this simplified ordering process draws upon the Kanban concept from Just-In-Time (JIT) inventory systems. JIT is a commonly used technique in the manufacturing industry that was popularized by Toyota, and a Kanban is a simple visual system that is used for implementing JIT. JIT/Kanbans have been shown to yield

considerable benefits in production settings, including simpler processes, more timely deliveries, increased responsiveness, increased firm profitability, and inventory reductions (Monden, 2011; Baudin, 2004; Fullerton & McWatters, 2001). In addition to manufacturing, Kanban/bin supply systems are being adapted elsewhere and have been shown to provide better inventory control in many healthcare settings, e.g., managing critical nursing supplies (Southwest solutions group, 2015) and other items (Graban, 2011). Rahn (2010) explains why the Kanban method has advantages over the commonly used PAR-level system for hospital material management (where items are replenished every period to bring inventories back to some base stock level). He emphasizes seven main advantages including the fact that no counting is needed, and that it promotes better inventory management practices. The primary disadvantage is that this approach might need more physical storage space.

The remainder of this chapter is structured as follows. First, the problem is described and the suggested ordering policies are explained. Next, we perform a storage space analysis at the clinic level, with a focus on cold storage requirements. In this section, the methodology and equations related to the different ordering policies are presented, and numerical examples are illustrated using real data from two countries – Benin and Niger. Third, we perform storage space analysis in vaccine transportation between different levels in the supply chain to investigate the effect of the proposed ordering polices. We end with a brief discussion of our conclusions.

4.2 PROBLEM DESCRIPTION

In this research, we focus solely on the ordering process at the clinic level where vaccinations occur. Currently, the vial is the ordering unit and a base-stock policy is applied. Each period the health worker counts the remaining vials of each vaccine, records these numbers and then orders the number of vials needed to return to an inventory level equal to the average demand during the replenishment cycle. Note that for some vaccines the shelf life is limited once the vaccine vial has been opened and any vaccine remaining after this period has to be discarded. Such wastage is referred to as open vial waste (OVW) and this has been studied by Lee et al. (2010), Dhamodharan & Proano (2012) and Mofrad et al. (2014). The demand forecast is first inflated by a factor to account for the percentage of OVW (where applicable) to compute the number of vials needed and a buffer factor is added to account for demand variability. Using a base stock level (in vials) equal to the average adjusted demand plus a 25% buffer is a standard recommendation of the WHO (World Health Organization, 2014).

The upper level health worker receives order requests from the clinics and then picks the corresponding vials for each clinic and prepares them for shipment. All of the vial counting for all of the vaccines at both the clinic and the upper level is done manually and there are ample opportunities for ordering and order fulfillment errors. Since manufactures distributed vaccine vials in inner packs that typically range in size from 10 to 200 vials in one inner pack depending on the vaccine type and manufacturer, we propose two ordering policies based on inner packs and compare them with the current policy, which uses a vial as the unit.

The first proposed policy is referred to as the inner pack unit ordering policy, where a clinic orders vaccines only in inner pack units. For a given vaccine, the clinic worker counts the number of unopened inner packs and individual vials in any open pack to determine the number

of vials remaining and then calculates the required number of vials based on the forecast demand. This policy still requires some counting of vials to obtain the number remaining, but since there is at most one open inner pack at any time for a given vaccine, the worker only has to count the number of remaining vials in this one inner pack. For example, if an inner pack contains 20 vials and we have one unopened inner pack and one open one with 11 vials in it, only the latter would be counted to determine the current inventory of 31 units. If we require 55 vials for the next cycle (typically, one month), this means we need to order 24 more vials. Since ordering is based on rounding up to the next full inner pack, two inner packs are ordered. At the upper level the order fulfillment process is even simpler because only full inner packs are handled and no individual vial counting is required.

The second policy is referred to as a kanban ordering policy, where each empty inner pack is set aside in a specified location. The worker only counts the number of empty inner packs at the location for each vaccine and orders enough material to replenish these. Alternatively, one might follow a process like the one common in many manufacturing environments where each container - or inner pack in our case - is placed in its own slot (possibly, a location that is marked with a prominently marked symbol or color). When the inner pack is completely emptied it is discarded and the slot is empty (or the symbol is exposed), and this represents the fact that a replacement is required for it, so that we order as many inner packs as there are empty slots. In this context, each inner pack corresponds to a Kanban bin and the number of bins replenished is equal to the number fully consumed. This Kanban ordering idea is borrowed from the traditional Kanban materials management system for lean and just-in-time production. It most closely resembles a signal Kanban (Monden, 2011). An example signal Kanban is shown in Figure 13 where there are three measles inner packs that are stored. At the

time of reorder the healthcare worker simply orders the number of inner packs equal to the number of empty storage locations. Thus, only one inner pack is ordered in case (a) and two are ordered in case (b).

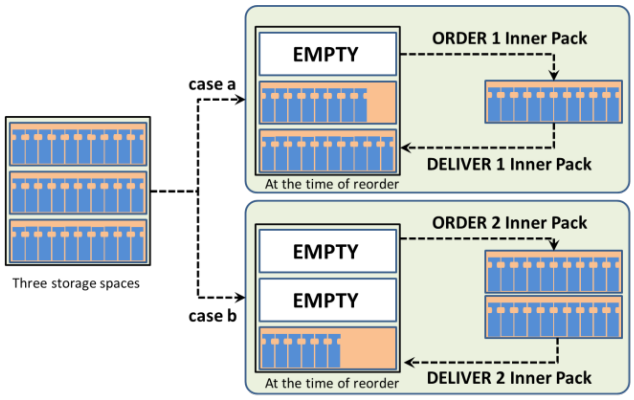


Figure 13. Signal Kanban example

The primary advantage of simplifying the ordering method is that it is easier to implement when the personnel involved might not be well trained, and it reduces potential errors that could occur during ordering. However, one drawback of the Kanban based idea is that it does require more storage space at the clinic. This is because the maximum number of vials stored under the current vial unit ordering method is equal to the order up to level, but if the inner pack unit or Kanban ordering policy is applied, the maximum amount stored will generally increase. In addition, a cold storage device used in transportation between points in the distribution chain may not be able to hold all of the vaccines, because filling the storage device with only inner packs both potentially increases the number of vials that must be transported and also decreases packing efficiency due to having to pack the physical dimensions of the inner pack rather than individual vials. In order to address these space issues, we evaluate the effect on storage space at the clinic level and in transportation in the following sections.

4.3 CLINIC STORAGE DEVICE ANALYSIS

Introducing the simplified ordering policies of the previous section generally leads to needing more storage space at the clinic because vaccines are now ordered in inner pack units. In order to evaluate the effect of the two proposed policies on incremental space requirements, we perform a clinic storage device analysis. To understand the true impact at a high level, we use real data to calculate the total number of storage devices needed across the entire set of clinics in a country in order to store vaccines for each policy, and we repeat these calculations for different inner pack sizes. Since a public health decision maker would not want the number of storage devices to increase significantly due to the resulting increase in system-wide costs, our goal is to also determine an inner pack size that results in only a modest increase in the required number of storage devices country-wide.

4.3.1 Methodology

The total number of storage device needed is estimated conservatively by summing the minimum number of storage devices required at each location for each ordering policy. This can be computed using several pieces of available information: the monthly demand, the average number of vaccination days per week, device storage volumes, and vaccine information such as dose(s) per patient, number of doses per vial and packed volume per vial. The first step is to estimate the average total number of doses needed per vaccination day for vaccine i at location j $(= s_{ij})$ as follows:

$$s_{ij} = \left\lceil \frac{d_j}{a_j} \right\rceil \times p_i \tag{49}$$

where d_j denotes the patients per month expected at location/local clinic j, a_j denotes the number of vaccination days per month at location j, and p_i denotes the doses per patient of vaccine i.

Next, we calculate the number of vials m_{ij} required per month for vaccine i at location j, as follows:

$$m_{ij} = \left\lceil \left\lceil \left(\frac{s_{ij}}{1 - ovw(s_{ij}, v_i)} \right) \times \frac{a_j}{v_i} \right\rceil \times (1 + b) \right\rceil \tag{50}$$

where v_i denotes the number of doses per vial of vaccine i, ovw is the open vial waste which is a function of s_{ij} and v_i, and b denotes the buffer value; the $(1 + b)$ term is used to add a buffer to account for variability in the patient arrival process.

Because m_{ij} is the number of vials required per month, anytime the inventory level is below m_{ij} at the beginning of the month, ordering needs to occur. Thus, $m_{ij} - 1$ is the largest number of vials that can be on hand when ordering occurs. Assume we use inner packs containing k vials. With our first (inner pack) ordering policy, we simply count the number of vials in any currently open inner pack (say, *x*) and the number of unopened inner packs (say, *y*) and if $ky + x < m_{ij}$ we place an order for $\lceil (m_{ij} - ky - x)/k \rceil$ inner packs.

With the second (Kanban) ordering policy, we have to be more careful. Recall that we order as many inner packs as the number fully consumed, and assume that the policy is implemented by assigning each inner pack a slot and ordering enough to fill each empty slot. Then the minimum number of slots to set aside (say *n*) is given by

$$n - 1 \geq \frac{m_{ij} - 1}{k} \tag{51}$$

$$n = \left\lceil \frac{m_{ij} - 1}{k} \right\rceil + 1 \tag{52}$$

It might seem that we could simply let $n = \lceil m_{ij}/k \rceil$ but this is not sufficient because we want to ensure that when there is a partially empty inner pack (as would often occur) at an ordering time, we order sufficient inventory. For example, suppose the inner pack size is 20, m_{ij} is 50, and we have two full inner packs plus one inner pack with 6 vials in it when we review the inventory prior to deciding on whether to place an order. If we only set $n = \lceil 50/20 \rceil = 3$ slots then we will not order any vaccines since all three slots are currently occupied (two by full inner packs and one by the inner pack with 6 vials). However, we will only have 46 vials on hand, which is below our desired inventory level. Thus, the + 1 term is needed to insure that the clinic always starts with the minimum required number of vials. Otherwise, a partially filled inner pack (in the extreme case, with as little as one vial in it) would result in us not placing an order to replenish that inner pack, which might cause the starting level of stock to be below the desired amount and increases the likelihood of a vaccine shortage during that cycle. Furthermore, we use $m_{ij} - 1$ rather than m_{ij} because in the case that $m_{ij} - 1$ is an integer multiple of the inner pack size, using m_{ij} could result in holding one more inner pack than is strictly necessary, because in this special case even if the last inner pack only has one vial remaining that is sufficient. For example, if the inner pack size is 20 and m_{ij} is 61, then using $n = \lceil m_{ij}/k \rceil + 1 = \lceil 61/20 \rceil + 1$ will result in using 5 slots. However, only 4 slots are actually required because even if the inner pack in the last slot contains only one vial we will have sufficient vial inventory for the month.

We made the assumption that vaccine vials are stored in inner packs in the storage device when the inner pack unit ordering policy or Kanban ordering policy is used. Therefore, even if only one vial is left in the inner pack the volume of one entire inner pack is still occupied. The

Kanban ordering policy needs sufficient space to store the number of inner packs required to provide m_{ij} vials and then one more inner pack because inner packs are only replaced once they are fully empty. The inner pack unit ordering policy also needs enough space to hold the number of inner packs required to provide m_{ij} vials, plus one, because at times one inner pack may have as few as one vial remaining but still occupies an entire inner pack's volume. For example, let $k = 10$ and $m_{ij} = 14$, then $\left\lceil \frac{m_{ij}-1}{k} \right\rceil + 1 = \left\lceil \frac{14-1}{10} \right\rceil + 1 = 3$, so space to hold three inner packs is needed. If there are 18 vials left at the time of reordering, no vaccine is ordered under the inner pack ordering policy (because 18 > 14), but one inner pack is ordered in the Kanban ordering policy (because one inner pack location is empty). If there are 13 vials left at the time of reordering, both policies order one inner pack. Thus, the Kanban and inner pack ordering policies both require sufficient space to store the same maximum number of inner packs although the average inventory level of the inner pack ordering policy will be lower.

To estimate the required vaccine storage volume for a vaccine we start with the packed volume per vial (which we define as g_i^o). For vaccines that require a diluent (a liquid that is used to reconstitute freeze dried vaccines), the diluent must also be stored in the storage device before it is used. We assume that 10% of a vaccine's diluent is stored in the storage device at any point in time. Thus, the net storage volume per vial of a vaccine, g_i, is given by

$$g_i = g_i^o + 0.1 l_i \tag{53}$$

where l_i denotes the packed diluent volume of vaccine i. Using an inner pack of k vials, we need a packed volume of $(g_i \times k)$ units of space per inner pack, and multiplying this by the number of inner packs required, we may estimate the minimum required volume of vaccine i at location j with inner packs of size k, denoted as r_{ijk}, via:

$$r_{ijk} = (g_i \times k) \times \left(\left\lceil \frac{m_{ij} - 1}{k} \right\rceil + 1 \right) \tag{54}$$

So, the corresponding estimate of the number of storage devices n_j needed at location j is given by

$$n_j = \left\lceil \frac{\sum_{i \in I} r_{ijk}}{c_j} \right\rceil \tag{55}$$

where c_j is the capacity of a storage device at location j and I is the index set of all vaccines. Summing these over $j \in J$, where J is the set of clinics, finds the total number of storage devices needed within an entire country. In particular, if k=1 for all vaccines $\sum_{j \in J} n_j$ is the total number of storage devices needed in the country using the vial unit ordering policy. In general, let $s = (i, k) \in S$, where S is the set of pairs of vaccine types and corresponding inner pack sizes. For example, if BCG uses an inner pack of size 20, measles one of size 10 and PCV one of size 50, then $S = \{(BCG, 20), (Measles, 10), (PCV, 50)\}$, and the total number of storage devices needed in the country, $N(S)$, may be estimated as:

$$N(S) = \left\lceil \sum_{j \in J} \frac{\sum_{(i,k) \in S} r_{ijk}}{c_j} \right\rceil \tag{56}$$

Note that in this particular capacity analysis we only consider clinic cold storage space and do not consider any transportation capacity issues.

4.3.2 Numerical example

We illustrate our approach by applying it to data from two countries: Benin and Niger. Table 18 provides summary data for these two countries. (Haidari et al., 2015; Lee et al., 2012)

Table 18. Summary data for Benin and Niger

	Benin	**Niger**
Number of local clinics	658	695
Number of vaccines	8	8
Vaccination days per month	5 – 28	16
Mean clinic demand (Range of clinic demands)	564 (100 - 3300)	1,083 (300 - 3,400)

Vaccine information for Benin and Niger is shown in Tables 19 and 20. Note that the same vaccine can have a different packed volume per vial in different countries because the vaccine might be supplied by a different manufacturer. The data also shows that different countries can require different numbers of doses of a particular vaccine.

Table 19. Vaccine information for Benin

Name	**Vaccine presentation**	**Doses/ vial**	**Packed vol./ vial(cc)**	**Doses /person**	**Diluent vol./ vial(cc)**	**Current inner pack size**
Tuberculosis	Lyophilized	20	21.09	1	12	50
Tetanus Toxoid	Liquid	10	25.41	2		10
Measles	Lyophilized	10	21.09	1	25	50
Oral Polio	Liquid	20	14.06	4		100
Yellow Fever	Lyophilized	10	25.41	1	25.4	10
DTC-HepB-Hib liquid	Liquid	2	9.92	3		100
PCV13	Liquid	1	17.13	3		50
Rotavirus	Liquid	1	13.5	2		50

*Note that the current inner pack size is inferred from the WHO vaccine database and vaccine information for Benin

Table 20. Vaccine Information for Niger

Name	Vaccine presentation	Doses/ vial	Packed vol./ vial(cc)	Doses /person	Diluent vol./ vial(cc)	Current inner pack size*
Tuberculosis	Lyophilized	20	24	1	14	50
Tetanus Toxoid	Liquid	10	30	3		10
Measles	Lyophilized	10	21.3	1	5	10
Oral Polio	Liquid	20	20	4		100
Yellow Fever	Lyophilized	10	25	1	6	10
DTC-HepB-Hib liquid	Liquid	1	16.8	3		50
PCV13	Liquid	1	12	3		50
Rotavirus	Liquid	1	45.9	3		10

*Note that the current inner pack size is inferred from the WHO vaccine database and vaccine information for Niger

The following analysis considers inner pack sizes of 10, 20, 50, and 100, which represent round numbers that are commonly seen in practice. The first analysis is done for Benin. If we set the inner pack sizes of all vaccines to be the same, the total number of storage devices needed and the annual operation costs are as follows:

Table 21. Total number of storage devices by inner pack size for Benin

	Vial unit ordering	Inner pack unit ordering/Kanban ordering			
Inner pack size (k)	1	10	20	50	100
Total number of storage devices	664	664	670	706	1117
Annual operation costs($)	521,535	521,535	526,545	555,593	898,018

As seen in Table 21, with k=10 there is no need to purchase any additional cold storage devices. With inner packs of k=20 vials for all vaccine, only six more storage devices are

needed and even when the inner pack has 50 vials there is only a modest increase in the number of additional storage devices needed.

Given that each vaccine has its own characteristics, it follows that the inner pack sizes of all vaccines need not be the same. To find a reasonable inner pack size for each vaccine, a marginal volume analysis was done for each vaccine, where the inner pack size of the selected vaccine increases but all of the others are set to 1. The results are shown in Table 22; e.g., for the measles vaccine, using k=10, 20, 50 and 100 result in marginal increases in volume of 4%, 9%, 25% and 55%, respectively, and we could pick a size depending on the percentage increase that we are willing to tolerate. We consider two such values, corresponding to marginal increase in volume of up to 10% and up to 20%. The orange colored cells indicate the inner pack size breakpoint for up to a 10% volume increase, while the blue colored cells represent the breakpoint for up to a 20% increase. If the breakpoints are the same for 10% and 20%, then only an orange colored cell is shown. For Tuberculosis, Tetanus Toxoid, Measles and Yellow Fever, the 10% and 20% breakpoint volume inner pack sizes are the same (=20).

Table 22. Marginal volume increase for each vaccine Benin

Vaccines		**1**	**10**	**20**	**50**	**100**
Tuberculosis	Volume	5,325	5,506	5,710	6,572	8,040
	Increase %	0%	3%	7%	23%	51%
Tetanus Toxoid	Volume	5,325	5,532	5,764	6,727	8,382
	Increase %	0%	4%	8%	26%	57%
Measles	Volume	5,325	5,545	5,783	6,669	8,259
	Increase %	0%	4%	9%	25%	55%
Oral Polio	Volume	5,325	5,439	5,568	6,101	7,017
	Increase %	0%	2%	5%	15%	32%
Yellow Fever	Volume	5,325	5,579	5,855	6,877	8,714
	Increase %	0%	5%	10%	29%	64%
DTC-HepB-Hib liquid	Volume	5,325	5,405	5,498	5,845	6,323
	Increase %	0%	1%	3%	10%	19%
PCV13	Volume	5,325	5,434	5,570	6,007	6,705
	Increase %	0%	2%	5%	13%	26%
Rotavirus	Volume	5,325	5,443	5,595	6,135	6,955
	Increase %	0%	2%	5%	15%	31%

Using the inner pack sizes corresponding to the 10% and 20% marginal increases in volume for each vaccine, the total number of storage devices needed is shown in Table 23, along with the results for the current inner pack size combination.

Table 23. The total number of storage devices by inner pack size Benin

	Vial unit ordering	**Inner pack unit ordering/Kanban ordering**						
Inner pack size	1	10	20	Up to 10%	Up to 20%	Current	50	100
Total number of storage devices	664	664	670	670	678	699	706	1,117
Annual operation costs($)	521,535	521,535	526,545	526,545	533,427	550,557	555,593	898,018

As seen in Table 23, with inner packs of k=50 for DTC-HepB-Hib and k=20 for all other vaccines (up to a 10% marginal volume increase) we still require the same number of additional storage devices (6) as the case where all inner packs are of size 20. On the other hand, using inner packs of k=100 for DTC-HepB-Hib, k=50 for Polio, PCV13 and Rotavirus, and k=20 for all other vaccines (up to a 20% marginal increase in volume) we require 14 additional storage devices. Finally, if we switched to an inner pack ordering or Kanban ordering policy while staying with the inner packs that are currently in use (as shown in Table 19), we would still need only 35 additional devices country-wide.

Conducting a similar analysis in Niger, we picked inner pack sizes for each vaccine with up to a 5% and up to a 10% marginal volume increase. Note that we did not consider a value of 20% because even with inner pack sizes of 100 there was only a 7% increase and vaccines do not typically come in inner packs larger than 100 vials (Table 24).

Table 24. Marginal volume increase for each vaccine Niger

Vaccines		1	10	20	50	100
Tuberculosis	Volume	19,788	19,813	19,841	20,275	21,093
	Increase%	0%	0%	0%	2%	7%
Tetanus Toxoid	Volume	19,788	19,788	19,788	20,194	20,863
	Increase%	0%	0%	0%	2%	5.4%
Measles	Volume	19,788	19,860	19,959	20,168	20,870
	Increase%	0%	0%	1%	2%	5.5%
Oral Polio	Volume	19,788	19,788	19,788	20,044	20,655
	Increase%	0%	0%	0%	1%	4%
Yellow Fever	Volume	19,788	19,873	19,988	20,235	21,059
	Increase%	00%	0%	1%	12%	6%
DTC-HepB-Hib liquid	Volume	19,788	19,788	19,788	20,017	20,180
	Increase%	0%	0%	0%	1%	2%
Rotavirus	Volume	19,788	19,788	19,788	20,412	20,858
	Increase%	0%	0%	0%	3%	5.4%
PCV13	Volume	19,788	19,813	19,841	19,951	20,068
	Increase%	0%	0%	0%	1%	1%

If up to a 5% and up to a 10% volume increase inner pack size for each vaccine are applied, the total number of storage devices needed is shown in Table 25. Table 25 also shows results for the current combination of inner pack sizes.

Table 25. Total number of storage devices by inner pack size for Niger

	Vial unit ordering	Inner pack unit ordering/kanban ordering					
Inner pack size (*k*)	1	10	20	Current	50	Up to 5%	100/ Up to 10%
Total number of storage devices	1,057	1,068	1,068	1,122	1,177	1,188	1,499
Annual operation costs($)	679,975	686,468	686,468	716,030	747,712	755,159	850,136

The Niger results indicate that using inner packs of up to 20 for all vaccines requires only eleven more storage devices over the entire country than with the current vial unit ordering policy; this is a very small increase. Note that this is less than the number of storage devices

needed if used the new ordering policies with the current set of inner pack sizes. Choosing inner packs of size 50 for all vaccines results in needing 120 more storage devices which represents only about a 10% increase in the total number of devices. If we increase the inner pack sizes up to 100 then there is a significant increase in the number of storage devices needed. We could also use a combination of inner packs of size 20 for all vaccines except PCV13 and DTC-HepB-Hib liquid where a size of 50 would be used (a larger inner pack is used for PCV13 and DTC-HepB-Hib liquid because both are relatively small volume and have high demand) This results in a need for 1,069 storage devices across the country, which is an increase of only twelve over the single vial ordering policy. Thus, ordering logistics in Niger can be greatly simplified from both the ordering and fulfillment viewpoints with very little impact on the number of storage devices needed countrywide at the clinic level.

4.4 TRANSPORTATION STORAGE SPACE ANALYSIS

So far, we have only considered clinic cold storage space and not transportation capacity. Typically, vaccines are transported to clinics in vaccine carriers, using small 4×4 vehicles, motorcycles, bicycles or even on foot. These vaccine carriers have limited storage space and given that inner packs take up more space in a carrier than individual vials, ordering policies that use an inner pack unit may require more storage devices in transportation, and specific devices might not be suitable in the first place. According to the WHO's specifications, the capacity of vaccine carriers which are used for vaccine vial transportation is between 0.5 and 5 liters (World Health Organization, 2010).

The BK-VC 1.7-CF which is used from the District distribution centers to clinics in Benin has a capacity of 1.7 liters. In Niger on the other hand, a 5 liter vaccine carrier is used (Assi et al., 2013). In addition, although the average volume of vaccines transported to a clinic might be similar, there is a higher degree of variation in the total volume required with the inner pack policies and the packing efficiency is worse since their replenishment unit is an inner pack. Therefore, we need to consider how using inner packs affects storage space requirements when transporting vials to clinics.

4.4.1 Simulation model

In order to examine the effect of using inner packs on transport capacity requirements, a model is developed using Microsoft Excel VBA to simulate a clinic's ordering policy. We assume that the daily demand follows a Poisson distribution, and values of these demands at each clinic j for each vaccine i are randomly generated using a mean value of s_{ij} (as given by (49)). Monthly orders are placed according to each of the ordering policies that we study. The simulation model has the following parameters: inner pack size, doses per vial, whether or not the vaccine experiences open vial waste, buffer percentage, annual number of patients served at the location, vaccination days per month, doses per patient, and ordering policy.

The model assumes that 1) the lead time is zero, 2) back orders are not allowed, 3) the vaccine shelf lives are long enough that expiration is not a problem, and 4) vaccines are ordered each month. We run the simulation using the inner pack sizes found from the previous section that analyzed storage device requirements at the clinic level. The output of the model is the number of vials or inner packs ordered each month for each vaccine type under each ordering

policy; this determines the total amount of vaccine that must be transported to the clinic from the next higher level, and hence, the required transportation storage capacity.

4.4.2 Methodology

The simulation model is run for 2000 months and for each month, and for each vaccine, it yields either the number of inner packs (for the two simplified policies that use an inner pack unit), or the number of vials ordered (for the current ordering policy). From this data, the volumes of the shipments are then calculated. Since the transportation storage devices should be able to transport the required vaccine amount of vaccine every month with a high probability, we specify the required total volume to be such that at least 95% of all orders (as estimated from the simulation output) can be successfully transported. This is estimated from the output of the simulation. Using this vaccine replenishment data and the capacity of each transportation storage device we then estimate the number of transportation storage devices required.

For the current ordering policy with vial ordering/storage, we decrease the available space in the device to account for its packing efficiency. For example, if the capacity of a storage device is 3 liters and the packing efficiency is 80%, the storage device can hold 2.4 liters of vaccine vials; thus, if our requirement was for 6 liters of vaccines, we would need 3 devices. With the two simplified ordering polices, we use a trial-and-error method for packing the required vaccine inner packs into the physical dimensions of the transport storage device, given their dimensions and the dimensions of the storage space in the device. While a more sophisticated approach such as a 3D bin packing algorithm could be used, we chose to use the simpler methods that might be used in practice by a healthcare worker in the field.

4.4.3 Numerical example and Result

The results from the simulation and the analysis are shown below for Benin. The transportation storage device commonly used at clinics in Benin (BK-VC 1.7-CF) has a vaccine storage volume of length 10 cm, width 10 cm and height 17 cm after it is packed with conditioned ice. The average annual patient demand, which is 550, is used to determine daily demand for doses of each vaccine. Since some of the current inner packs (Tuberculosis, Measles, DTC-HepB-Hib and PCV13) are too large to be held in the BK-VC 1.7-CF, assessing the simplified ordering policies with these inner packs is impossible, and the only option is to order in vial units. However, as we saw in the storage device space analysis, 10- or 20-vial inner packs could be considered with very little increase in clinic storage requirements. Table 26 shows the actual inner pack dimensions for the 10-vial inner packs. Note that the new dimensions are calculated based on the current vial diameter and height.

Table 26. 10 vial inner pack dimensions

Vaccines	Tuberculosis	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib	PCV13	Rota
Length(cm)	9.25	10.6	9.25	7.5	10.6	9	8.95	7.3
Width(cm)	3.8	4.7	3.8	2.5	4.7	2.98	3.68	3.4
Height(cm)	6	5.1	6	7.5	5.1	3.7	4.1	6.9

Using the current vial unit ordering policy, we need 6.39 liters to cover all orders with a probability of 0.95, and 6.55 liters with 0.99 probability. Using the Kanban ordering policy or inner pack unit ordering policy with 10-vial inner packs for all vaccines, 6.49 liters are needed to cover all orders with the 0.95 probability, and 6.67 liters with 0.99 probability. Table 27 shows the corresponding number of inner packs of each vaccine for the simplified ordering policies.

Table 27. Number of inner packs for the simplified ordering polices

Vaccines	Tuberculosis	Tetanus	Measles	Oral Polio	Yellow Fever	DTC-HepB-Hib	PCV13	Rota
Kanban ordering	2	1	2	1	2	8	14	12
Inner pack unit ordering	2	1	2	1	2	7	16	11

Table 28 shows the number of storage devices required to hold 6.39 liters of vaccine vials for different packing efficiencies. For example, if an effective 80% of device storage space is available, five storage devices are needed. In fact, if the packing efficiency is between 80% and 90%, five storage devices will suffice.

Table 28. Number of storage devices required to hold 6.39 liters of vaccine vials

Packing efficiency	70%	80%	90%	100%
The number of the storage devices	6	5	5	4

When 10-vial inner pack vaccines are used, we estimated that six storage devices are required for both the Kanban ordering policy and the inner pack unit ordering policy to cover 95% of vaccine delivery. With 20-vial inner packs, seven storage devices are required for both policies.

Clearly, if the inner pack size cannot be changed, the simplified ordering policies are not practical. However, if 10 or 20 vial inner pack can be used, one or two more additional transportation storage devices (vaccine carriers) would be required at each clinic.

4.5 DISCUSSION AND CONCLUSIONS

Ordering vaccines in inner pack quantities has many advantages over single vial ordering including convenience in managing inventories, fewer errors in counting and ordering, and reduced order fulfillment effort. If vaccines are stored within an inner pack, a health worker can easily distinguish vaccines from each other and more readily find the particular vaccine that the worker is looking for because there is vaccine information on the outside face of the inner pack. In addition, at the upper level distribution center, the complicated vial counting process to supply clinics will be replaced by a much simpler process of picking one, or counting just a few inner packs. Counting errors at the upper levels will decrease and order preparation and distribution time will be saved. EPI vaccines are not particularly expensive, so there is no real disadvantage to holding more vaccines at the clinic level, as long as there is sufficient storage space.

The results from Benin and Niger indicate that while there is no common inner pack size that is best for all vaccines, if we use inner packs of size 10 or 20 for all vaccines only a few more storage devices are needed. Thus, even though these simplified ordering policies increase the storage volume needed, if we choose the proper inner pack size these negative consequences can be minimized such that the additional number of storage devices needed is very small (on the order of 1%). In terms of transportation storage space, the proposed ordering policies are not practical without changing the inner pack size. However, if 10- or 20-vial inner packs are used across all vaccines, one or two more storage devices in transportation will be required to service orders with a high probability. Note that in general, a vaccine carrier is inexpensive (e.g., the 2009 price of a BK-VC 1.7-CF is US$ 12.00), so purchasing one or two devices would be very affordable for a clinic. But if transportation resources are constrained it might become necessary for an additional trip to a clinic in order to carry additional vaccine carriers. In this case the

transportation cost will increase and it might be difficult to implement due to time and resource limitations.

In conclusion, we recommend adapting simplified ordering polices based on well-known lean concepts (that are widely used in manufacturing) to a major public health sector. There are several key managerial insights relating to this recommendation. First, only replenishing using inner pack quantities reduces logistical effort and potential ordering errors at multiple levels of the supply chain. This is particularly valuable in the context of lower and middle income countries as many of the workers involved in the vaccine supply chains in these countries are not well trained in logistics systems operations. Second, while the average inventory levels do increase slightly with the simplified policies, the increase is minor and only causes minor increases (less than a few percent) in the number of cold storage devices needed at facilities if the inner pack sizes are carefully chosen. Third, transport logistics are also not impacted significantly. Thus, we can achieve significant benefits from simplified ordering policies with modest increases in operational costs by selecting proper vaccine inner pack sizes.

5.0 REDESIGN OF VACCINE DISTRIBUTION NETWORKS IN LOW AND MIDDLE-INCOME COUNTRIES

5.1 INTRODUCTION

In many low and middle income countries supported by the Expanded Program on Immunization, vaccines are distributed through a legacy medical supply chain. The legacy medical supply chain consists of traditional medical facilities including a central distribution center for the country, regional hospitals, district hospitals, and clinics. Their locations and connections within the supply chain network (SCN) have typically been determined based on political boundaries or the existing administrative hierarchy. Since the distribution network is not optimized, the legacy medical supply chain is not necessarily a cost-efficient one.

In this chapter, we separate the cold chain for vaccine distribution from the legacy medical supply chain and address it independently. The primary characteristic of this chain is that it requires cold storage and transportation of a narrowly defined set of vaccines at controlled temperatures of between 2 and 8°C. When the vaccine supply chain is separated from the medical supply chain, redesigning it can be approached via mathematical models. In this chapter, a mixed integer programming (MIP) model for designing the vaccine supply chain network is introduced. As our analysis with real data shows, the solution of this problem can be quite difficult, and an evolutionary strategy (ES) is therefore proposed to solve the network design problem.

The remainder of this chapter is structured as follows. Section 2 describes the problem. Section 3 presents the mixed integer mathematical model and Section 4 proposes the evolutionary strategy to solve the problem. In Section 5, sensitivity analysis is performed. Section 6 introduces a looping factor that is applied to the transport vehicle routing and illustrates how to apply it. We talk about how to improve the ES in section 7. In section 8, we describe how to use the results from the ES to enhance the MIP performance. Each section presents its own numerical examples based on real data to illustrate the problem and solution characteristics.

5.2 PROBLEM DESCRIPTION

EPI vaccines from foreign manufacturers typically enter a country via air or sea and are initially stored in a central distribution center. Then via intermediate distribution centers, they are transported to local clinics, where actual vaccinations take place. The legacy medical supply chains in most countries have a 3, 4 or 5 tier arborescent structure. For instance, in a typical 4-tier vaccine supply chain, vaccines move from the central distribution center to regional distribution centers, and from a regional distribution center to district distribution centers, and finally, from a district distribution center to clinics. However, since the distance from the main source node, (the central distribution center), to a final sink node (a local clinic) varies widely and the supply chain network design was not optimized, this hierarchical and arborescent structure does not guarantee an optimal distribution scheme.

Our goal is to send vaccines from one fixed source node to a set of fixed sink nodes efficiently. If intermediate distribution centers (hub distribution centers) through which vaccines

are transported from a source node to sink nodes are selected properly, the distribution network will be more efficient. While the current network has a fixed number of tiers, this does not have to be the case in general and we do not assume any such restriction. That is, vaccines can be supplied to local clinics from the central distribution center through any number of hub distribution centers, or even directly. A hub distribution center is a facility that stores vaccines and supplies vaccines to local clinics as well as other hubs. Only the local clinic is assumed not to have any distribution role. Hub distribution centers are selected from the current regional and district distribution centers, which serve as a set of candidates.

This research considers several different storages devices at each facility and different transportation modes/vehicles for transporting vaccines between facilities. Each facility is allowed to choose its own storage devices for vaccines as well as its own transportation vehicles. These storage devices have different capacities and a facility can have different storage devices to hold its required volume of vaccines. Note that the storage capacity can be changed only in discrete increments corresponding to additional devices. As with storage devices, there are several types of capacitated transportation vehicles from which a facility can choose one. In addition, we consider a replenishment/trip frequency along with vehicle capacity. For example, if the total required volume at a facility in a year is 120 units and the replenishment frequency is once a month, the required storage volume at the facility is 10 units, but if the replenishment frequency is once every three months, 30 units of storage capacity is needed. The trip frequency also works in the same way, e.g., if each replenishment must move 10 units and the capacity of the vehicle is 5 units, then two trips will be required per replenishment. With respect to cost, we consider transportation cost, storage cost, and facility operation cost. Transportation cost is calculated using a travel distance between two nodes and increases discretely according to the

number of vehicle trips needed to deliver the required volume. Storage cost is also related to the volume of required vaccines and increases discretely according to the number of storage devices required to store the vaccines. Even though there are several vaccines handled, only the total volume of vaccines affects the capacity of transportation and storage so that we only consider the total volume of vaccines along arcs and at nodes. Facility operation costs are incurred when a facility is open.

In this research, we decide the locations of hub distribution centers, the flows from the central distribution center to local clinics through hub distribution centers, the storage devices and their numbers at each facility, the transportation vehicles used and the number of trips required for each vaccine flow between facilities, taking into account the assumed trip frequency for each connection between supply chain levels.

We make the following assumptions to reflect a real vaccine supply chain:

(1) Only local clinics have demand and demands at each clinic are fixed based on the population served by the clinic.

(2) The location of the central distribution center does not change.

(3) A hub distribution center can only be located at the current regional and district distribution center locations.

(4) Every local clinic is supplied via a hub distribution center (or directly from the central distribution center).

(5) Each operational facility has exactly one inbound flow except the central distribution center, which has none.

(6) Enough vaccine should be supplied to clinics to satisfy all demand.

(7) If a hub is supplying another hub and is supplied by the central distribution center, it is replenished quarterly.

(8) If a hub is supplied by another hub, it is replenished monthly.

(9) The replenishment frequency of local clinics is once a month.

(10) The storage device type at a local clinic is given.

(11) There is a required 25% buffer at each location so that the total required storage volume is inflated by a factor of 1.25.

(12) If more than one trip to a lower level facility is required, it does not change the replenishment frequency to the lower level facility, i.e., we assume that the multiple trips are done on the same day.

The supply chain network design problem is well-known to the operations research community and there are many papers as well as reviews on this topic. The *p*-median problem, the uncapacitated facility location problem (UFLP), and the capacitated facility location problem (CFLP) are introduced as the basic network location problems in many papers [e.g., (Klose & Drexl, 2005), (Melo, Nickel, & Saldanha-Da-Gama, 2009) and (Mirchandani, 1990)]. These location problems have been mostly studied for single level systems (Şahin & Süral, 2007). Various extensions to these basic models have been derived, such as the capacitated facility location problem with single sourcing (CFLPSS), the two-stage capacitated facility location problem (TSCFLP), and the multi-commodity or multi-activity uncapacitated facility location problem (MUFLP) (KloseA. & DrexlA., 2005). Mirchandani et al. discuss a stochastic variant of the *p*-median problem (Mirchandani, Oudjit, & Wong, 1985). The uncapacitated facility location/network design problem (UFLNDP) is introduced by Daskin et al. (Daskin, Hurter, & VanBuer, 1993) and the capacitated facility location/network design problem (CFLNDP) is

introduced by Melkote et al. (Melkote & Daskin, 2001). With UFLNDP and CFLNDP, where the facility location and network design problems are combined, similar to the problem in this chapter, it is often more economical to change the configuration of the underlying network rather than adding and locating new facilities (Melkote & Daskin, 2001). If a network has hierarchical features, there are two basic distinct MIP models: flow-based and assignment-based formulations (Şahin & Süral, 2007). Narula and Ogbu examine flow-based formulations for multi-flow systems (Narula & Ogbu, 1979) and Şahin et al. construct a two-level multi-flow assignment-based model (Şahin, Süral, & Meral, 2007).

More recently, hub location models have received considerable attention (Klose & Drexl, 2005). Algorithms for solving the uncapacitated hub location problem (UHLP) have been developed by several researchers [e.g., (Klincewicz, 1996), (Ernst & Krishnamoorthy, 1998), and (Hamacher, 2000)]. The capacitated case has been studied by several researchers, e.g., (Aykin, 1994) and (Ebery, Krishnamoorthy, Ernst, & Boland, 2000). Unlike the general models or papers mentioned above, recent work has considered more complexities to cope with a more realistic variety of situations. For example, Rahmaniani and Ghaderi have worked on a combined facility location and network design problem with multiple types of capacitated links and suggested a fix-and-optimize heuristic based on the firefly algorithm (Rahmaniani & Ghaderi, 2013). Kalaitzidou et al. optimize multiechelon supply chain networks with generalized production and warehousing nodes using a mathematical programming model (Kalaitzidou, Longinidis, Tsiakis, & Georgiadis, 2014). In this model, the optimization procedure decides which mid echelon locations produce items and which ones only distribute items.

Regarding applying genetic algorithms to supply chain problems, the first was an application to a transportation problem used a nonstandard genetic algorithm for solving linear

and nonlinear transportation problems (Michalewicz, Vignaux, & Hobbs, 1991). The authors used a matrix-based representation to represent a transportation tree. Since then, there have been several studies on transportation problems (Bielli, Caramia, & Carotenuto, 2002; Gen, Altiparmak, & Lin, 2006; Altiparmak, F; Gen, M; Lin, L; Karaoglan, I, 2009). For example, Altiparmak et al. presented a solution procedure based on a steady-state genetic algorithm with a new encoding structure for the design of a single-source, multi-product, multi-stage SCN (Altiparmak, F; Gen, M; Lin, L; Karaoglan, I, 2009). They extended the priority-based encoding of the transportation tree to a multi-product case. Firoozi et al. solve a three level hierarchical supply chain, which is modeled with non-linear MIP, using a genetic algorithm (Firoozi, Ismail, Ariafar, Tang, & Ariffin, 2013). Izadi and Kimiagrari solve the location-allocation problem with an unknown demand function using a genetic algorithm and a Monte Carlo simulation approach (Izadi & Kimiagari, 2014).

5.3 MIP FORMULATION

To formulate the problem we define the following notation:

Index sets

C: Central distribution center =$\{0\}$

H: Hub distribution centers =$\{1,2,\ldots,|H|\}$

I: Local clinics = $\{|H|+1,\ldots,N\}$

E: Edges:$(i,j)|i \in C \cup H, j \in H \cup I; i \neq j$

V: Vertices: $C \cup H \cup I$

L: Levels: {central (=0), hub (=1), local clinic (=2)}

T: Transportation vehicles: {cold truck (=0), 4×4 truck (=1), motorbike (=2)}

R: Storage devices: {cold room (=0), regional device (=1), district device (=2), local clinic device (=3)}

F: Replenishment frequency: {Quarterly (=0), Monthly (=1)}

Parameters

C_{ijt}^{T}: Transportation cost per km of vehicle type t from location i to location j ; $(i,j) \in E; t \in T$

C_r^S: Annual storage cost per storage device r; $r \in R$

C_l^F: Annual facility cost when the facility is level l; $l \in L$

P_t^T: Transportation capacity per trip of vehicle t; $t \in T$

P_r^S: Storage capacity of device r; $r \in R$

G_f: Annual number of replenishments $f \in F$ (=4 if k=0; =12 if k=1)

S: Buffer stock factor for vaccines stored at a location

D_{ij}: Distance (km) between location i and location j ; $(i,j) \in E$

B_j: Annual demand (B_j<0, $j \in I$) or supply (B_j>0, $j \in C$) volume at location j; $B_j = 0$ for $j \in H$

Variables

X_{ij}: Annual flow (volume) of vaccines from location i to location j ; $(i,j) \in E$

$W_j \in \{0,1\}$: 1 if a location j is open, 0 otherwise; $j \in V$

Y_{jrf}: Number of storage devices of type r at location j with replenishment frequency f; $j \in V, r \in R,\ f \in F$

Z_{ijtf}: Number of vehicle trips per replenishment from location i to location j using vehicle type t with replenishment frequency f; $(i,j) \in E, t \in T, f \in F$

$V_j \in \{0,1\}$: 1 if a location j has monthly replenishment frequency, 0 otherwise; $j \in H \cup I$

$U_{ij} \in \{0,1\}$: 1 if vaccines flow from location i to location j, 0 otherwise; $(i,j) \in E$

Our formulation is:

$$Min \sum_{(i,j)\in E}\sum_{t\in T}\sum_{f\in F} 2C_{ijt}^{T} G_f D_{ij} Z_{ijtf} + \sum_{j\in V}\sum_{f\in F}\sum_{r\in R} C_r^S Y_{jrf} + C_0 W_0 + \sum_{j\in H} C_1^F W_j + \sum_{j\in I} C_2^F W_j \quad (57)$$

subject to

$$\sum_{j\in V:(i,j)\in E} X_{ij} - \sum_{j\in V:(j,i)\in E} X_{ji} = B_i \qquad for\ \forall i \in V \quad (58)$$

$$\sum_{t\in T}\sum_{f\in F} P_t^T G_f Z_{ijtf} \geq X_{ij} \qquad for\ \forall\ (i,j) \in E \quad (59)$$

$$\sum_{r\in R}\sum_{f\in F} P_r^S G_f Y_{jrf} \geq (1+S) \sum_{i\in C\cup H:(i,j)\in E} X_{ij} \qquad for\ \forall j \in V \quad (60)$$

$$MW_j \geq \sum_{i\in C\cup H:(i,j)\in E} X_{ij} + \sum_{i\in H\cup I:(j,i)\in E} X_{ji} \qquad for\ \forall j \in H \quad (61)$$

$$X_{ij} \leq MU_{ij} \qquad for\ \forall\ (i,j) \in E \quad (62)$$

$$\sum_{i\in C\cup H:(i,j)\in E} U_{ij} \leq 1 \qquad for\ \forall j \in H \cup I \quad (63)$$

$$\sum_{r\in R}\sum_{f\in F} Y_{jrf} \leq MW_j \qquad for\ \forall j \in H \quad (64)$$

$$\sum_{r\in R} Y_{jr1} \leq MV_j \qquad for\ \forall j \in H \quad (65)$$

$$\sum_{r\in R} Y_{jr0} \leq M(1-V_j) \qquad for\ \forall j \in H \quad (66)$$

$$X_{ij} \leq MV_j \qquad for\ \forall i,j \in H \quad (67)$$

$$V_i \leq 2 - U_{0i} - \frac{\sum_{j\in H} U_{ij}}{|H|} \qquad for\ \forall i \in H \quad (68)$$

$$W_i = 1 \qquad for\ \forall i \in C \cup I \quad (69)$$

$$V_i = 1 \qquad for\ \forall i \in I \quad (70)$$

$$Y_{000} = 1 \quad (71)$$

$$X_{ij} \geq 0 \quad for\ \forall (i,j) \in E \quad (72)$$

$$W_j \in \{0,1\} \quad for\ \forall j \in V \quad (73)$$

$$Y_{jrf} \in \{0,1,2,\dots\} \quad for\ \forall j \in V, \forall r \in R, \forall f \in F \quad (74)$$

$$Z_{ijtf} \in \{0,1,2,\dots\} \quad for\ \forall (i,j) \in E, \forall t \in T, \forall f \in F \quad (75)$$

$$V_j \in \{0,1\} \quad for\ \forall j \in H \cup I \quad (76)$$

$$U_{ij} \in \{0,1\} \quad for\ \forall (i,j) \in E \quad (77)$$

where M is a large number.

The objective function (57) consists of three terms: Annual round-trip transportation cost, annual storage cost and annual facility cost. Constraint (58) is a conservation of flow equation, where the inbound flow to a hub facility is equal to its outbound flow and the inbound flow to a clinic is equal to its total demand. Constraint (59) ensures that if an edge representing transportation between two locations is used, there are sufficient trips during each replenishment using the selected vehicle to transport the total volume of vaccines required to be transported along the edge. Constraint (60) ensures that a facility is able to have enough capacity (number of storage devices) to store the total amount of vaccines before the next replenishment (including any buffer stock). Constraint (61) states that if a facility is closed, the inbound flow to the facility and outbound flow from the facility is 0. Constraint (62) states that if an edge is not used, there is no flow on the edge. Constraint (63) ensures that each hub and clinic has at most one inflow. Constraint (64) allows a facility to have storage devices only when a facility is open. Constraints (65) and (66) stipulate that the Y_{jrf} variable has the appropriate value corresponding to the selected replenishment frequency at facility j. Constraint (67) states that the trip or replenishment frequency at a hub that is supplied by another hub is once a month. Constraint (68) guarantees that a hub that is supplied by the center gets replenished once every quarter. Note that the quantity $\frac{\sum_{j \in H} U_{ij}}{|H|}$ is a positive fraction between 0 and 1 so that if there is shipment from the

central store to hub i, then V_i must be equal to zero (quarterly replenishments); otherwise it could be 0 or 1. Constraint (69) ensures that the central distribution center and all local clinics are open, while Constraint (70) ensures that all local clinics have monthly replenishments. Finally, Constraint (71) states that the central distribution center must have a cold room.

The above formulation can be used to solve the network problem optimally, but as the problem size becomes bigger, the computational time increases exponentially. For example, suppose there are three kinds of storage devices and three kinds of transportation vehicles, along with five candidate hubs and 125 clinic locations. For this problem, the MIP formulation leads to approximately 102,500 integer variables. If we increase the number of candidate hubs and clinics by a factor of four (which would be quite representative of the structure in many countries), the number of integer variables increases by a factor of 16 to approximately 1,627,000. Even if the computational effort is not directly proportional to the number of integer variables, the additional computational time required to solve the model can be prohibitive. For example, the largest problem we can solve with the MIP formulation has 210 locations including 13 candidate hubs. It takes 196 hours using IMB ILOG CPLEX 12.6 on a computer with an Intel Xeon CPU E5450 3.00 GHz with 20.0 GB memory (also note that different combinations of CPLEX parameters were evaluated before choosing the one that minimized computational time). This problem represents only two of the eight regions in Niger. Many network problems have a similar issue with dramatic increases in computational effort as the size of the problem gets larger. Often, this issue is addressed by developing heuristics based on Lagrangian relaxation, linear programming, or constructive methods, or by using so-called metaheuristics (Melo, Nickel, & Saldanha-Da-Gama, 2009).

In the next section, we propose a metaheuristic that uses an evolutionary strategy (ES) to obtain a good solution to the network problem in a reasonable amount of time.

5.4 EVOLUTIONARY STRATEGY ALGORITHM

5.4.1 Introduction

An Evolutionary Strategy (ES) is a population based algorithm that is related to genetic algorithms, which were developed independently (Whitley, 1994) and have been used to solve large network problems (Altiparmaka, F; Genb, M; Linb, L; Paksoy, T, 2006; H. Aytug , M. Khouja & F. E. Vergara, 2003; Altiparmak, F; Gen, M; Lin, L; Karaoglan, I, 2009). ES is based on the work of Rechenberg and Schwefel (Schwefel, 1975).

An ES can be a good candidate for solving the vaccine distribution network design problem based on the problem's characteristics and its likely optimal network structure: (a) most clinics will tend to be supplied from the nearest open hub, (b) the number of candidate hubs is relatively small; e.g., Niger has 40 candidate hubs even though there are 644 clinic locations, and (c) the optimal network has a tree structure which is not very deep and its branches can be clustered. Fact (a) implies that the ES does not need to have all connection information for the entire network and that the network structure from the central distribution center to the hubs is more critical (this is discussed in more detail later). Facts (a) and (b) permit the design of a simple ES representation that facilitates ES operations such as crossover and mutation, and can decrease the evaluation time of a candidate solution. Fact (c) is a good feature to have for a

population based method such as ES because the ES operations can be effective at finding improved solutions in successive iterations of the algorithm.

There are two types of ES: $(\mu + \lambda)$-ES and (μ, λ)-ES. The (μ, λ)-ES is closer to the canonical genetic algorithm, where μ parents produce λ offspring and only the best μ of the λ offspring replace the μ parents ($\mu < \lambda$). On the other hand, in the $(\mu + \lambda)$-ES, μ parents produce λ offspring, and the population is then reduced again to μ parents by selecting the best solutions from among both the parents and offspring (Whitley, 1994). In this chapter, a $(\mu + \lambda)$-ES is used to apply high selective pressure. Goldberg and Deb have shown that replacing the worst member of the population tends to produce higher selective pressure (Goldberg & Deb, 1991).

One of the reasons for long computation times for the MIP model is that the vaccine volumes handled at the hubs cannot be fixed before the network structure is set. In the ES, a chromosome decides the network structure from the central storage location to the hubs and the local clinics are automatically assigned to the nearest open hub to then complete the entire network. Throughout the network, the amount of vaccine that must be handled at each hub location is decided and then appropriate transportation and storage devices are selected. Note that the best possible result found using the ES representation is not guaranteed to be an optimal solution since the local clinics do not necessarily have to be connected to the nearest open hubs. This is because clinic to hub assignments that result in more travel distance may result in lower overall cost of storage device costs. For example, if Hub A can eliminate one storage device by not servicing one of its clinics and there is another hub, say Hub B, which has sufficient storage space to supply the clinic which was supplied by Hub A. If the cost of doing this from Hub B is lower than the cost of using one more storage device at Hub A, then the local clinic (which was

supplied by Hub A) can now be supplied by Hub B. However, it is reasonable that in an optimal solution one could expect many of the local clinics to be connected to the nearest open hubs. Therefore, even though the ES does not guarantee that it can solve the network problem optimally, it can hopefully produce a very good solution. In addition, if we fix the portion of the network structure that does not include the clinics, solving the problem is much easier and computation times decrease dramatically because the number of clinics greatly exceeds the number of candidate hub locations.

In this section, an evolutionary strategy is introduced in order to address the computational problems associated with the MIP formulation of the vaccine network problems, and numerical examples are presented to illustrate the approach and demonstrate its effectiveness.

5.4.2 An ES for vaccine supply chain network design

5.4.2.1 The ES procedure

Figure 14 shows the flow of the ES. The upper part shows the ES procedures and the lower part presents the post processing that occurs after terminating the ES. The ES basically follows a Genitor $(\mu + \lambda)$ strategy. However, here we initially generate a population of size 2μ and then choose the best μ of these for higher selective pressure. Moreover, we continue to maintain a population of size μ until termination, where the members are ranked at the beginning of each iteration in descending order of their fitness/performance. In the crossover step we select one parent at random from the population and another from the top α_1% of the population. As we will explain, because of how the crossover is performed the number of offspring chromosomes produced (λ_1) is not the same at each iteration. Similar to crossover, in the mutation step we elect

one chromosome at random from the population and another from the top α_2% of the population, these generate λ_2=2 new chromosomes. The $\lambda = \lambda_1 + \lambda_2$ new offspring generated at the iteration are then added to the existing μ members and the entire population is then re-ranked and reduced to a new set of μ members by eliminating the ones at the bottom. This completes one iteration and we repeat the process with the new population. The process is terminated either when there is no change in the population's best α_3% of chromosomes over T successive iterations or after T_{max} iterations. In the post-processing step we then solve the MIP with the central-to-hub structure fixed according to the best chromosome in order to obtain the assignment of clinics to hubs.

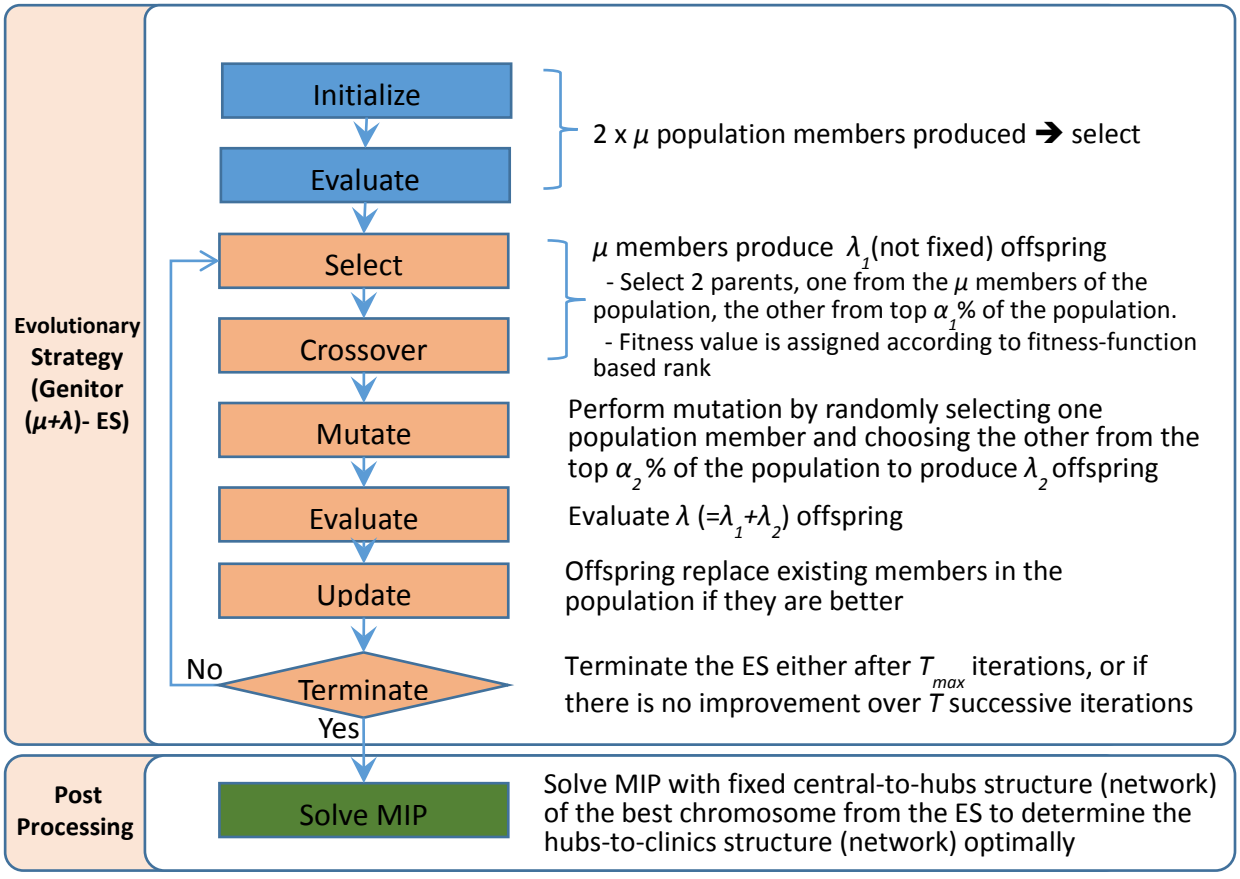


Figure 14. Evolution strategy for the network problem

The solution representation and initialization are now described in more detail. A matrix-based representation, which falls into the category of edge-based representations, is used to represent the solutions. A chromosome is represented by an $(n+1) \times n$ matrix, where n is the number of hubs. Rows in the matrix correspond to the outbound flow from hubs and columns to the inbound flow into hubs. That is, $a_{ij} = 1$ implies that hub i supplies hub j, and $a_{ij} = 0$ implies that hub i and hub j are not connected, where a_{ij} is an element of the matrix in row i and column j. The first row represents the central distribution center. Figure 15 shows examples of two chromosomes for $n = 6$.

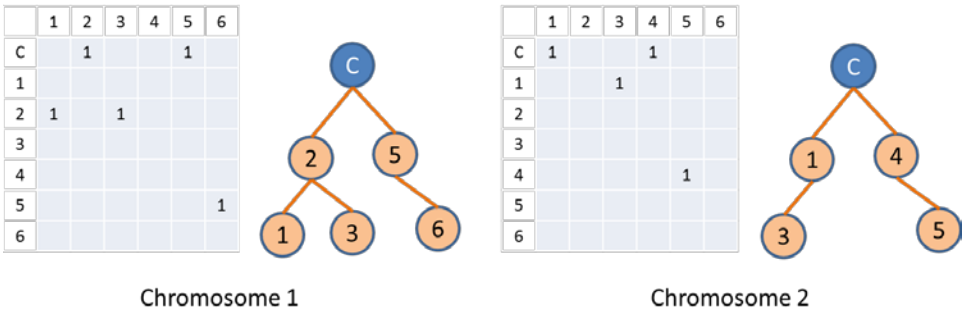


Figure 15. Chromosome examples

Note that since each location can be supplied by exactly one location, each column sum is less than or equal to one.

For initializing a new chromosome, we use the following steps:

Step 1. The values of the elements in the first row are decided randomly, with each column having a probability p_1 of being selected and assigned a value of 1. This fixes which hubs are supplied from the central distribution center. If hub i is supplied from the central store, it is an open hub and i is inserted into the open hub set ($= O$). Other hubs that are not in O are assigned to the complementary set L.

Step 2. Next, wechoose an open hub, say $j \in O$, update $O = O\backslash\{j\}$, and randomly decide whether j supplies other hubs or not, where p_2 is the probability that hub j supplies other hubs and (1-p_2) the probability that it does not. If j is selected to supply other hubs, then a hub $k \in L$ is selected to be supplied from j with probability p_3 and we update $O = O \cup \{k\}$ and $L = L\backslash\{k\}$ with each selection k.

Step 3. Repeat step 2 until $O = \emptyset$.

5.4.2.2 Evaluation

A chromosome c has network information from the central store to the hubs, but does not have information from hubs to clinics. Therefore, for evaluation of a chromosome, each clinic is temporarily assigned to the nearest open hub and the flows into each hub are determined. Based on the flows into each location, the transportation volume along each connected arc and the storage volume at each open facility are decided across the entire network. This is because once the flows are fixed, the demand (or volume of vaccine to be stored) at each location is also known. Based on this volume, we know the storage and transportation volumes required at each node and along each arc that is used, respectively. Once these volumes are fixed, the performance of the chromosome($= E(c)$) is evaluated as follows:

$$E(c) = \sum_{(i,j)\in E} 2D_{ij} \min_{t\in T, f\in F}\{C_{itf}^{T} G_f \left\lceil \frac{X_{ij}}{P_t^T G_f} \right\rceil\} + \sum_{j\in V} \min_{r\in R, f\in F}\{C_r^S \left\lceil \frac{(1+S)\sum_{i\in C\cup H:(i,j)\in E} X_{ij}}{P_r^S G_f} \right\rceil\} + C_0 W_0 + \sum_{j\in H} C_1^F W_j + \sum_{j\in I} C_2^F W_j \quad (78)$$

The first term, where the lowest cost transportation vehicle and the shipping frequency are decided, determines the annual transportation cost. The second, where the lowest cost storage device and replenishment frequency are decided, determines the total annual storage cost, and

the last term determines the annual facility cost. Note that the network structure determines the values of W_j and U_{ij}.

5.4.2.3 Selection

After a chromosome is evaluated, a fitness value is assigned based on the chromosome's rank in the population. In the selection step for crossover, two parents are selected: one is chosen randomly from the whole population and the other is chosen randomly from the top $\alpha_1\%$ of the population, based on the fitness rank. The reason why we choose one parent from the top $\alpha_1\%$ is to apply higher selective pressure. Similarly, two chromosomes are also selected for mutation: one is randomly chosen from the top $\alpha_2\%$ of the population and the other is randomly chosen from the entire population.

5.4.2.4 Crossover

A 1-point crossover is performed between the two parents, where the crossover point is randomly selected. Swapping the fragments occurs only in the first row within the column and the other n rows follow the crossover from the first rows. That is, the crossover point divides the network tree into two sub-trees and then sub-trees are swapped between the two parents. For example, in Figure 16, if chromosomes 1 and 2 at the top are swapped between column 3 and 4, the crossover results are shown. In this example there is no duplication of hubs and both offspring are feasible, but in general, this need not be the case. If redundant hubs exist across the two sub-trees, we might have a hub that is supplied from two upper level facilities (or a cycle may occur). For instance, in Figure 17, if node 2 in chromosome 1 supplies nodes 1 and 4 instead of nodes 1 and 3, then one of the offspring, chromosome $1'$, has a cycle, where node 4 is supplied by both the central node and node 2. Node 4 can select only one supply node: either the

central node or node 2 as shown in the right hand side of the figure. Thus, chromosome $1'$ and chromosome 2 produce three offspring. Note that there might be several redundant hubs when crossover is performed and because every redundant hub increases the number of offspring by a factor of 2. This is why $\lambda_1$is not fixed. If there are no redundant hubs, the two parents produce two offspring ($\lambda_1 = 2$), but if there are in general, $n(\geq 1)$ redundant hubs in a child chromosome after the crossover, it is replaced by $2 \times n$ new child chormosomes.

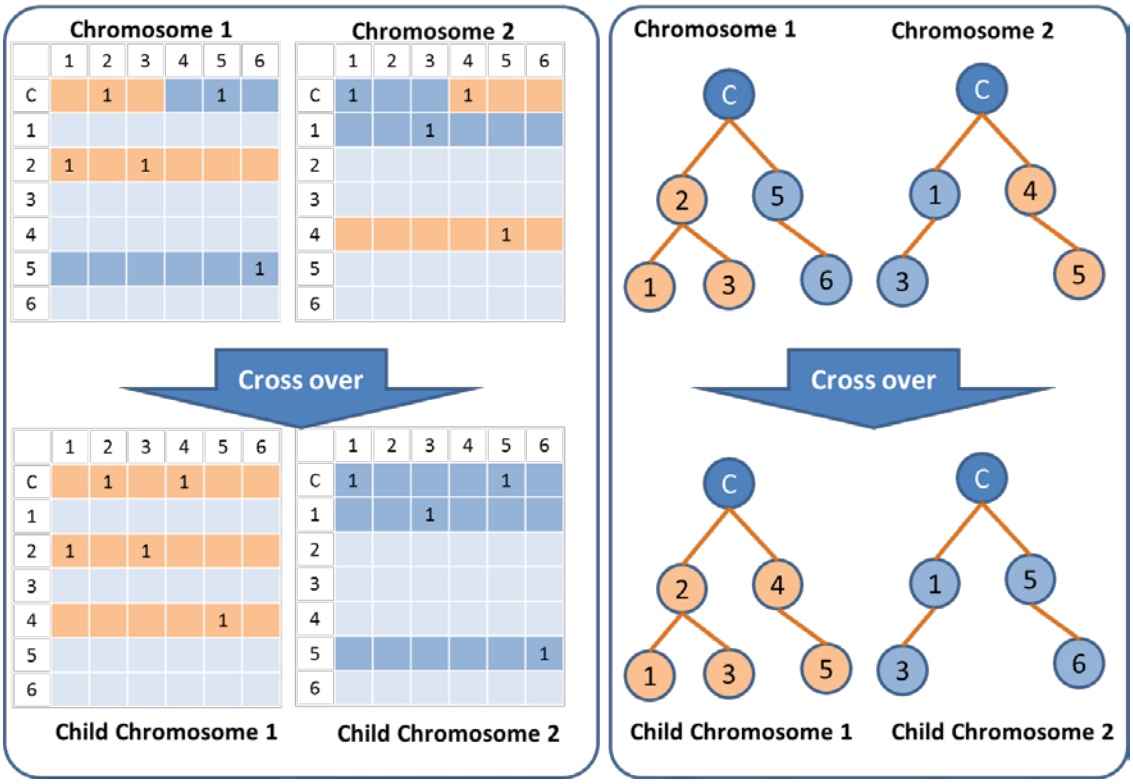


Figure 16. Crossover example

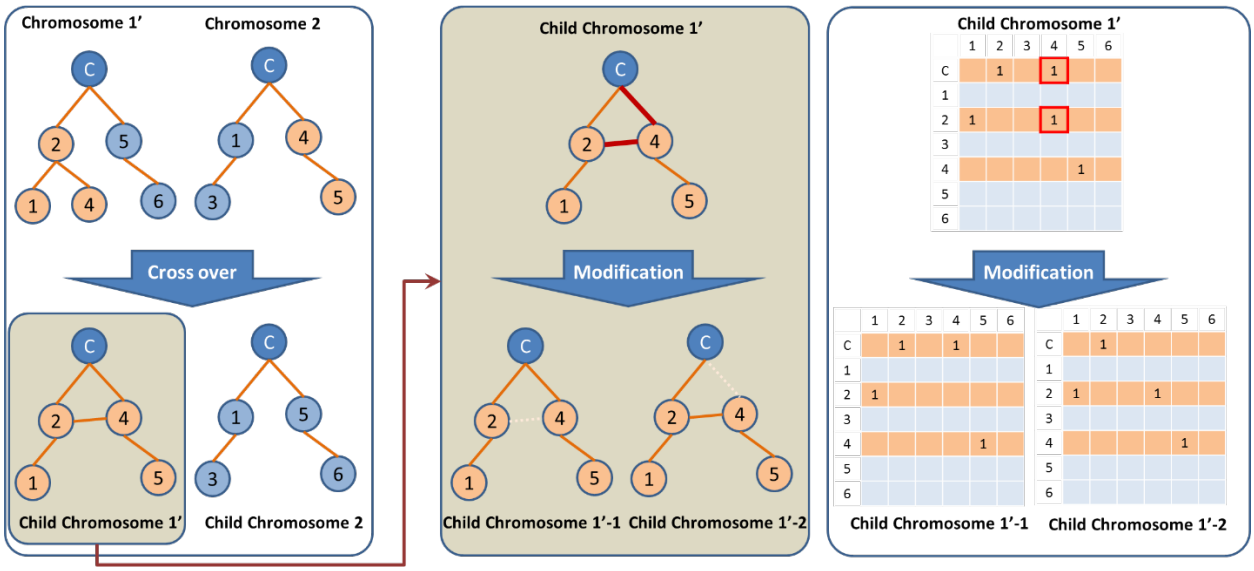


Figure 17. Example of handling a redundant hub in crossover

5.4.2.5 Mutation

Mutation occurs with probability p_m at every iteration. Two chromosomes are selected for mutation: one from the top $\alpha_2\%$ of the population and the other randomly selected from the entire population. There are three options for mutation: (1) eliminating a hub, (2) adding a hub, and (3) exchanging hubs. Each type of mutation has the same probability of occurring. Figure 18 illustrates these mutations. If option (1) is selected, a hub selected randomly from the open hubs is removed from the network. If a hub (say, Hub A) is removed, then any hubs supplied by Hub A are now supplied directly from the location that supplied Hub A. If option (2) is chosen, a hub (say, Hub B) among the closed hubs and a hub (say, Hub C) among the open hubs (including the central distribution center) are selected, and Hub C and Hub B are connected. In option (3), two hubs among the open hubs are selected and their positions are exchanged.

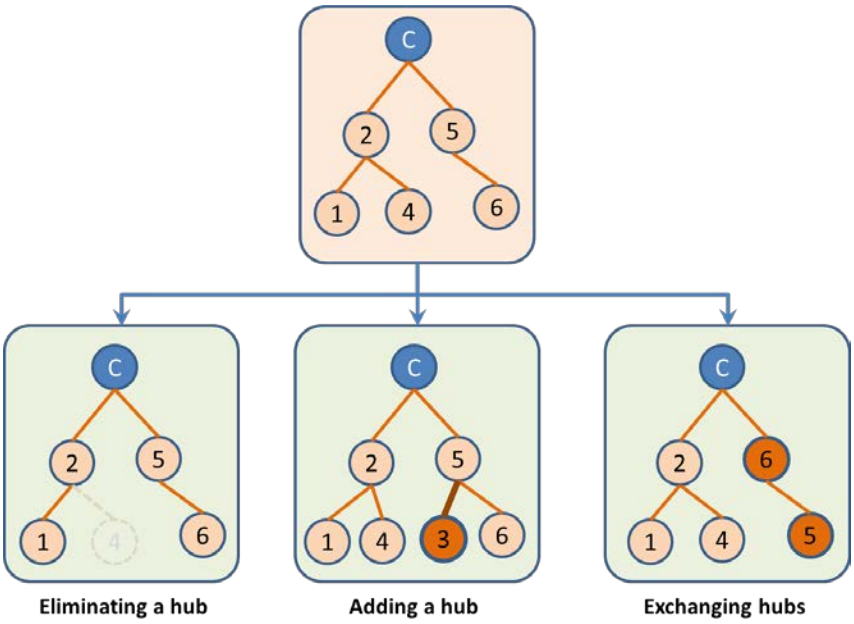


Figure 18. Mutation

5.4.2.6 Termination and optimization

After evaluation, if no change is observed in the top α_3% of the population over T successive iterations, or we have reached our iteration limit of T_{max}, the algorithm is terminated. Although the best chromosome has the minimum cost only the network structure from the central location to the hubs is considered for optimization, and the network from the hubs and the local clinics is not optimized. However, if the network from the central location to the hubs is fixed, assigning the local clinics to the hubs optimally is relatively easy. This is done by solving an MIP problem with the upper level of the network structure being fixed to the one that the ES produces. Consider an open location $i \in C \cup H$ and link i-j, $j \in H$ along which vaccines flow, as determined by the ES and define:

$W_j^E \in \{0,1\}$: 1 if location j is open, 0 otherwise; $j \in H$

$U_{ij}^E \in \{0,1\}$: 1 if vaccines flow from location i to location j, 0 otherwise; $i \in C \cup H$ and $j \in H$

The following additional constraints are added to the MIP Model in section 3.

$$U_{ij} = U_{ij}^{E} \qquad for\ \forall\ i \in C \cup H \text{ and } \forall j \in H \tag{79}$$

$$W_j = W_j^{E} \qquad for\ \forall j \in H \tag{80}$$

5.4.3 Numerical example

5.4.3.1 Niger

The proposed approach is applied to a subset (2 regions) of the Niger distribution network. Table 29 provides summary data for this subset of the Niger distribution network. Information on vaccines, transportation, storage and facilities is shown in Tables 30 through 33.

Table 29. Summary data for Niger

	Number
Region and District distribution centers	13
Clinics	196
Vaccines	8
Transportation device types	3
Storage device types	4

Table 30. Vaccine information for Niger

Name	Vaccine presentation	Doses/vial	Packed vol./ vial(cc)	Doses /person
Tuberculosis	Lyophilized	20	24	1
Tetanus Toxoid	Liquid	10	30	3
Measles	Lyophilized	10	21.3	1
Oral Polio	Liquid	20	20	4
Yellow Fever	Lyophilized	10	25	1
DTC-HepB-Hib liquid	Liquid	1	16.8	3
PCV13	Liquid	1	12	3
Rotavirus	Liquid	1	45.9	3

Table 31. Transportation information for Niger

Vehicle Type	Capacity (L)	Cost ($/km)
Cold truck	9,293	0.97
4x4 Truck	172	0.54
Motorbike	5	0.23

Table 32. Storage information for Niger

Device Type	Capacity (L)	Cost ($/year)
Cold room	18,000	8,116
Regional level device	1,843	1,582
District level device	76	600
Clinic level device	35	596

Table 33. Facility information for Niger

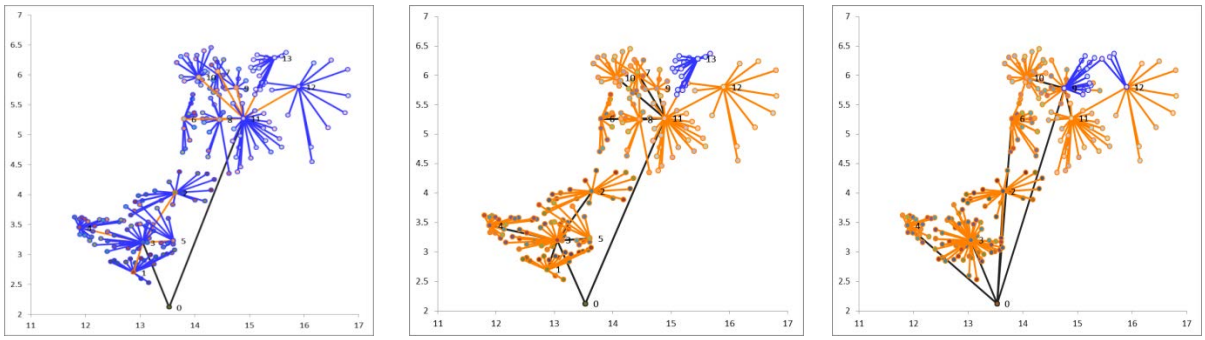
Facility type	Cost ($/year)
Central	40,000
Region	13,000
District/Hub	4,500
Clinic	800

Note that capacity and cost of transportation vehicles and storage devices at a particular level are weighted average values based on the equipment currently used at that level. For example, if there are 1,000 units of a 40-liter storage device and 600 units of a 20-liter storage device across the clinic level, the storage device assigned to the clinic level is assigned a capacity of 32.5 (=(1000×40+600×20)/1600) liters. This procedure is in order to simplify the problem. If we were to include every currently used vehicle and device type in the model as an option this would dramatically increase the computational effort. Facility cost is estimated based on labor and building operation costs.

This subnetwork has one central distribution center, along with 13 regional and district distribution centers, which are potential hubs. Table 6 provides three different network design results for the network. The first is the cost of the original network with the currently assigned vehicles and storage devices for the routes and locations, respectively. The second still uses the original network structure, that is, all the facilities are open and vaccines are distributed using the current routes, but vehicles and storage devices are optimally assigned to each route and each facility. The last is the network that is optimized for structure as well as devices using the original MIP in Section 5.3. Figure 19 shows the resulting graphs for each network. Black lines imply the use of cold trucks, orange lines correspond to 4×4 trucks, and blue lines to motorbikes.

Table 34. Network cost for Niger

Network	Total cost	Transportation cost	Storage cost	Facility cost	Computation time
Original Network	961,014	394,852	293,862	272,300	
Original Network with optimized devices	660,330	140,064	247,966	272,300	≤ 1 sec
Optimized Network	605,193	135,107	237,286	232,800	196 hours



Original Network | Original Network with optimized devices | Optimized Network

Figure 19. Network graphs for Niger

The annual cost of the original network is $961,014. Maintaining the original network structure but optimizing the transportation vehicles and storage devices used reduces the costs to $660,330. Thus, if we assign the transportation vehicles and storage devices to the facilities more appropriately, a cost savings of about 30% is possible for this subset of the Niger network. These savings come mostly from reduced transportation costs. If we solve this network problem optimally using the MIP described in Section 5.3, the total cost is $605,193, which is almost another 10% in additional savings and around 37% in savings from the original network. However, the computation time required to solve the problem optimally was 196 hours. The computational experiments were done using a computer with an Intel Xeon CPU E5450 3.00 GHz processor and 20.0 GB of RAM. Since the whole Niger network has 40 candidate hubs and 644 clinics, solving the entire network with this computer in a reasonable amount of time is not possible.

This same problem was also solved using the ES to fix the central-to-hub network combined with the MIP post processing to get the clinic to hub assignment. Table 35 shows the results of the ES + post processing for six different values of μ (the population size), where each of the six runs has 30 replications, each with different random number seeds. The ES input parameters are shown in Table 36. Note that extensive pilot tests were run for a range of parameter values and these values were chosen because the pilot testing indicated that this set performed best. The mean, standard deviation and minimum values across these 30 replicates along with the run times are reported. We also report the number of replicates in which the best solution found by the ES is also the optimal solution of the MIP (=Frequency of optimum).

Table 35. ES results

Population	10	25	50	100	300	600
Min	605,193	605,193	605,193	605,193	605,193	605,193
Avg	606,910	606,595	606,347	606,030	605,901	605,946
SD	1,807	972	760	424	433	311
Frequency of optimum	2	1	1	3	6	2
Run time for 30 replications (sec)	1,114	1,122	1,383	1,744	1,957	2,354

Table 36. ES parameter settings

Parameter	Value
μ	(10, 25, 50, 100, 300, 600)
p_m	100%
α_1	10
α_2	20
α_3	50
λ_2	2
p_1	20%
p_2	40%
p_3	20%
T	100
T_{max}	1000

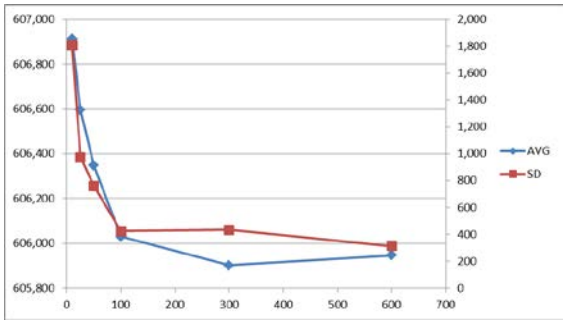


Figure 20. ES results for Niger

With $\mu \geq 100$, the ES provides stable results (Figure 20) in terms of the average quality of the best solution in the population. An analysis of variance indicates that there is no

significant difference between the solutions found by population sizes over 100 and the *t*-tests between different populations indicate that the poulation sizes that are over 100 have a significantly different average than those with population sizes less than 100. Thus, a population size of 100 or more is preferable although there is no advantage to making it larger than 100. For $\mu \geq 100$, the value of the solution found is on average about \$606,000, which is 0.14% higher than the cost found by the MIP. Recall that the ES does not assign clinics to hubs optimally, and therefore the best solution found by the ES is not guaranteed to be the optimal one found by solving the MIP. In this example, each experimental run has 30 replications and in all cases the minimum cost found by at least one of the replicates was equal to the optimal value of \$605,193 from the MIP. Each run takes 15 to 30 minutes to run 30 replications, which is a huge decrease in computation time compared to directly solving the original MIP.

Since the clinics are assigned to the nearest hub in the ES evaluation step, the best ES solution is not necessarily the same as the optimal solution of the MIP. Before deciding the final network, replications are required to get the best solution. From the example of this section, regardless of the size of the population, the minimum solution across 30 replications was the same in all cases. So instead of increasing the size of the population, increasing the number of replication is a better strategy.

5.4.3.2 Additional examples

In order to further evaluate the performance of the ES, similar experiments, using a population size of 100 for the ES, are performed for a subset of the networks found in three countries: Benin, Country A, and Country B. (Note that we use Country A and B instead of the actual country names because the Ministries of Health in those countries did not give us permission to use their country names – while the Ministries of Health in Benin and Niger did

give permission to use their names.) The parameter settings for the ES are the same as with Niger. Table 37 provides summary data for the network subsets of these three countries. The results are shown in table 38. In the Benin and Country A cases, the ES consistently found the optimal solutions. The average ES cost for Country B is 213,692, which is 0.1% more than the optimal solution.

Table 37. Summary data for Benin, Country A, and Country B

	Benin	Country A	Country B
Region and District distribution centers	13	10	11
Clinics	114	106	130
Vaccines	8	7	7
Transportation device types	3	3	3
Storage device types	4	4	4

Table 38. Results for Benin, Country A, and Country B

	Benin	Country A	Country B
Original Network	158,330	771,290	294,739
Original Network with optimized devices	157,052	771,290	291,103
Optimized Network	142,543	593,326	213,422
ES result (average of 30 replications)	142,543[1)]	593,326[1)]	213,692[1)]
ES Run time for 30 replications (sec)	460	319	630

[1)] These instances are relatively small, so the ES yields the same result for all 30 replications.

These smaller test problems have been used to demonstrate the effectiveness of the ES since the optimal solution can be determined for these smaller problems. However, the ES was created to find solutions to larger problems which the MIP model cannot solve in a reasonable amount of time. Thus, we now examine country-level problems for four countries, which the MIP model cannot solve in real time: Niger, Benin, Country A, and Country B. Table 39 provides summary data for these four countries. The parameter settings are the same as with the

previous Niger example except that the iteration limit is now set to 5000 (as opposed to 1000). The results are shown in Table 40.

Table 39. Number of locations for Niger, Benin, Country A, and Country B

	Niger	Benin	Country A	Country B
Region and District distribution centers	41	87	141	81
Clinics	644	658	2733	851

Table 40. Country level results for Niger Benin, Country A, and Country B

	Niger	Benin	Country A	Country B
Original Network (A)	2,989,490	791,164	11,182,800	6,987,500
Original Network with optimized devices	2,054,260	788,913	11,150,900	6,647,460
Best ES result (B)	1,903,500	718,898	8,710,000	5,414,090
Average	1,907,716	721,146	8,730,283	5,425,201
Standard deviation	4,057	1,294	11,870	17,900
Savings ((A-B)/A×100%)	36%	9%	22%	23%
ES Run time for 30 replications	3.7 hours	5.9 hours	30.1 hours	21.5 hours

5.4.4 Discussion

The ES can obtain excellent solutions to the network problem in a very reasonable amount of computational time. Given that we cannot solve these large problems optimally in a reasonable amount of time, it is not possible to objectively evaluate the quality of the ES solution to these problems. However, since the ES did well on smaller examples where we could indeed verify optimality, it is reasonable to conclude that that these solutions are likely to be very good. This

performance may be explained in terms of the following structural features of the vaccine distribution network.

1. A vaccine network does not have many candidate hubs relative to the total number of nodes in the network because the vast majority of nodes correspond to clinic locations.
2. Clinics are often assigned to the nearest open hub in an optimal solution.
3. The optimal network is not very deep.
4. An optimal network has a tree structure.

In addition, the following design features of the ES help it to find a good solution in a reasonable amount of time.

1. The ES constructs the network structure only from a central distribution center to hubs.
2. Clinics are heuristically assigned to the nearest open hub in the ES (although we allow ourselves the option of changing this in the post-processing step).
3. The crossover occurs between hubs supplied by a central distribution center.

5.5 SENSITIVITY ANALYSIS

The vaccine distribution network has three associated cost parameters - storage, transportation and facility costs - that are calculated based on storage device cost per year, transportation cost per trip and facility cost per year, respectively. They are fixed values in the model but in practice it might not be possible to ascertain exact values for these. In order to investigate the effects of cost variation on the network structure, we perform a sensitivity analysis around these cost estimates. One cost element at a time is perturbed, while the other two other are fixed. Each cost element is altered from 10% to 1,000% of the baseline value (with the other two maintained at

their baseline values). Subsets of the Niger, Benin, Country A and Country B vaccine distribution networks are used with the MIP. For Niger a larger problem with 2 regions, which is used in section 5.4.3.1,is also considered, but with the ES (which will likely provide at least a near-optimal solution), since running the MIP for this several times would take an inordinate amount of time. Since the MIP can provide the optimal network, we can readily observe the impact of the changes. Table 41 shows the number of candidate hubs and clinics in the four countries.

Table 41. Country information for sensitivity analysis

Country	Niger	Benin	Country B	Country A
Number of candidate hubs	5	13	11	10
Number. of clinics	86	114	130	106

Our interest is to study how the network changes according to how the costs vary. Therefore, we focus on the number of open hubs, the number of hubs supplied by a central distribution center and the number of levels.

5.5.1 Results

Table 42 shows the results of the sensitivity analysis for Niger (one district) which are obtained via the MIP. It indicates that changes in storage device costs have no effect on the network design but changes in transportation and facility cost can alter the network structure. As the transportation cost per trip increases from 10% to 1000% of its nominal value, the number of hubs increases. In the situation where the transportation cost is low, frequent trips are preferred and fewer hubs are open. When transportation costs are high, opening more hubs can reduce

costs by decreasing the number of trips required. The effect of changes in facility cost per year has an opposite effect to transportation cost changes. Higher facility costs decrease the number of open hubs (with higher transportation costs) and lower facility costs increase the number of open hubs (with lower transportation costs). Tables 43-45 show the sensitivity analysis results for subsets of the Benin, Country B and Country A networks that were considered. These results show trends similar to those obtained for Niger.

Table 42. Sensitivity analysis results for Niger (Dosso Province)

Cost Setting	Storage	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	3	3	3	3	3	3	3	3	3
	Number of levels	3	3	3	3	3	3	3	3	3
Cost setting	Transportation	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	1	1	3	3	3	4	4	5	5
	Number of levels	3	3	3	3	3	3	3	3	3
Cost setting	Facility	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	5	5	4	3	3	3	3	1	1
	Number of levels	3	3	3	3	3	3	3	3	3

Table 43. Sensitivity analysis results for Benin

Cost settings	Storage	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	5	5	5	5	4	4	3	3	3
	Number of levels	3	3	3	3	3	3	3	3	3
Cost settings	Transportation	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	1	2	3	3	4	5	5	5	7
	Number of levels	3	3	3	3	3	3	3	3	3
Cost settings	Facility	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	5	5	5	4	4	4	3	2	1
	Number of levels	3	3	3	3	3	3	3	3	3

Table 44. Sensitivity analysis results for Country B

Cost settings	Storage	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	6	6	6	6	6	6	6	6	5
	Number of levels	3	3	3	3	3	3	3	3	3

Cost settings	Transportation	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	2	2	4	5	6	6	6	8	9
	Number of levels	3	3	3	3	3	3	3	3	3

Cost settings	Facility	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	9	8	6	6	6	5	4	2	2
	Number of levels	3	3	3	3	3	3	3	3	3

Table 45. Sensitivity analysis results for Country A

Cost settings	Storage	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	2	2	2	2	2	2	2	2	2
	Number of levels	3	3	3	3	3	3	3	3	3

Cost settings	Transportation	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	1	1	2	2	2	2	2	2	2
	Number of levels	3	3	3	3	3	3	3	3	3

Cost settings	Facility	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	2	2	2	2	2	2	2	1	1
	Number of levels	3	3	3	3	3	3	3	3	3

The Niger network instance includes only one of its eight districts, so the three level network is optimal even though the cost factors are altered. This makes it impossible to see any changes in the network's depth. In order to examine this further, we also study a problem instance with two districts of Niger, which has 13 candidate hubs and 196 clinics. This instance can be solved by the MIP but it takes around 8 hours to get the optimal solution, so the ES is

used to obtain the best solution. The results are shown in Table 46. As the storage device cost increases, the number of levels decreases and the number of hubs decreases. This is because higher storage costs restrict the sizes of the open hubs and reduce the number of levels desired. As the transportation cost per trip increases, the number of hubs increases and the number of levels increases. This is because higher transportation costs call for shorter trips and the number of levels and hubs increase in order to reduce the trip distance. As the facility costs increase, the number of hubs and the number of levels decrease. In this case, in order to save costs, the network is forced to not open hubs and this leads to fewer levels. These increases and decreases exhibit monotonic behavior.

Table 46. Sensitivity analysis results for Niger (two provinces)

Cost settings	Storage	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	9	9	8	8	8	7	7	6	4
	Number of levels	5	5	5	5	5	5	5	3	3

Cost settings	Transportation	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	2	2	6	6	8	10	10	13	13
	Number of levels	3	3	3	4	5	5	5	6	7

Cost settings	Facility	10%	20%	50%	67%	100%	150%	200%	500%	1000%
Results	Number of hubs	11	10	10	10	8	7	5	2	2
	Number of levels	5	5	5	5	5	5	4	3	3

5.6 APPLYING A LOOPING FACTOR

5.6.1 Introduction

The current model assumes that a vaccine transportation vehicle visits only one place and returns to the original point of departure. In practice, the vehicle may visit several locations during one trip as long as it has enough capacity to carry all required vaccines. In order to add travel routes between the central warehouse and hubs, vehicle routing constraints are required to be added to the MIP model. However, the vehicle routing problem (VRP) is known to be an NP-Hard problem. If we add VRP constraints into the current MIP model, it is not possible to solve it in reasonable time for even small networks. So a two-step procedure is proposed for adding vehicle routing. First, the network problem is solved using the MIP formulation or the ES procedure. Once the network is fixed and the locations supplied by each of the hubs are decided, a vehicle routing problem from each hub to its delivery locations is solved in order to optimize the travel routes for that hub. Since there may be several hubs, the number of VRPs solved would be equal to the number of hubs (plus one for the central warehouse).

The introduction of vehicle routing to the network problem leads to a decrease in the transportation cost of the network because vehicles travel less than in a network where we assume that all trips are point-to-point. Thus the network structure obtained from solving our MIP (or by using the ES procedure) may be improved with the decreased transportation costs. However, we do not actually know these costs until the network is fully solved. We therefore use an estimate of the transportation cost for the optimization by applying a multiplicative looping factor, which is computed as the ratio of the transportation cost with vehicle routing to the transportation cost with all point-to-point travel. The transportation costs from the hub to each of

its delivery locations are then multiplied by this looping factor. The network design problem is then solved again using these lower transportation costs. Figure 21 shows an example of the looping factor calculation. Location D supplies locations 1-5. If a vehicle visits one place per trip, the total distance is 132 (left side of Figure 21). When the vehicle has two big loops (right side of Figure 21), the total distance is 93. Thus, the looping factor is calculated to be 0.705 (=93/132).

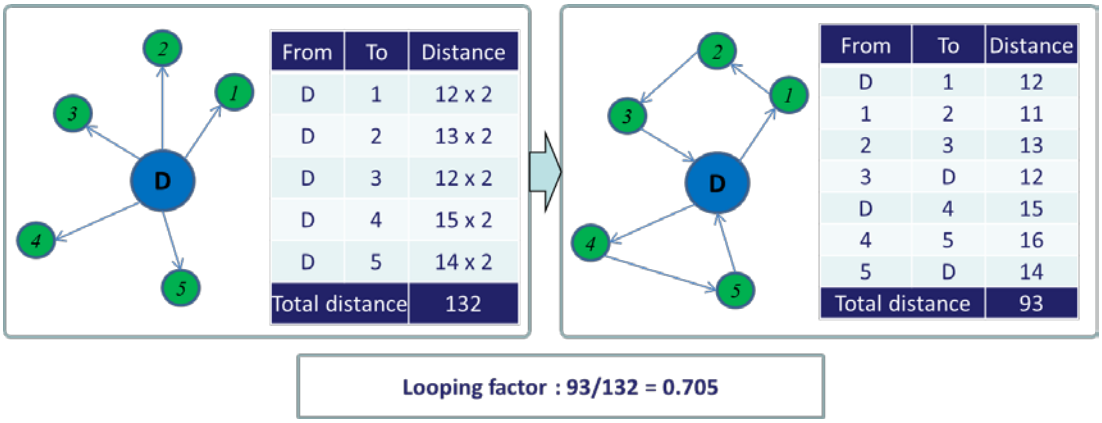


Figure 21. Looping factor example

Two issues arise when we solve the network design problem again. First, the central distribution center and each of the hubs has its own looping factor, and the transportation costs between a hub and its delivery locations are each multiplied by the hub's looping factor. The second issue is that the network structure obtained from the MIP or the ES procedure does not use all routes, so only a few vehicle routing paths are available after solving the VRPs. Therefore we assume that the network has representative looping factors depending on where the VRP origin and destinations are. We group the VRP deliveries in the network into three categories – central-to-hubs, hub-to-hubs and hub-to-clinics, and assume that there is a representative looping

factor corresponding to each of these categories.. Each representative looping factor is computed as the average of all looping factors computed by the different VRPs within each category. For example, consider the third category. Suppose there are five hubs with each one only supplying clinics, and suppose their looping factors are found to be 0.35, 0.4, 0.38, 0.42 and 0.45. Then the representative looping factor for hub-clinic deliveries is 0.4 (the average of these five values), and the transportation cost for deliveries from any hub to any clinic is multiplied by 0.4.

5.6.2 Procedure

After finding an initial network structure using the MIP or the ES, looping factors are calculated. However, once the network problem with the lower transportation costs is solved, the network structure originally obtained might change. If this happens, a fresh set of looping factors are computed for the new network and the procedure is repeated until there is no change in the network. That is, it is an iterative procedure, as shown in Figure 22.

- STEP 0: Use the MIP or the ES to obtain the network structure $\{N\}$. Looping factors are then obtained by solving VRPs resulting from $\{N\}$ and the "true" cost of the network (assuming we use these routes) is estimated as Z; this is done by multiplying each point-to-point transportation cost in the network by its looping factor.
- STEP 1: The network problem is re-solved with these looping factors using the MIP or the ES. If the structure of the new network $\{N_{new}\}$ is identical to $\{N\}$, we stop and the current network structure is the best we can find. If the network structure has changed, the VRPs resulting from this new structure $\{N_{new}\}$ are solved and new looping factors obtained. The "true" cost of the network $\{N_{new}\}$ is estimated as Z_{new} by multiplying the

original point-to-point transportation costs in the network by the appropriate looping factors

- STEP 2: If $Z_{new} \geq Z$ then the new network $\{N_{new}\}$ is not better and we stop with $\{N\}$ as the best structure we can find. If $Z_{new} < Z$ we have a better network, so we redefine $\{N\} \equiv \{N_{new}\}$, $Z = Z_{new}$ and return to Step 1.

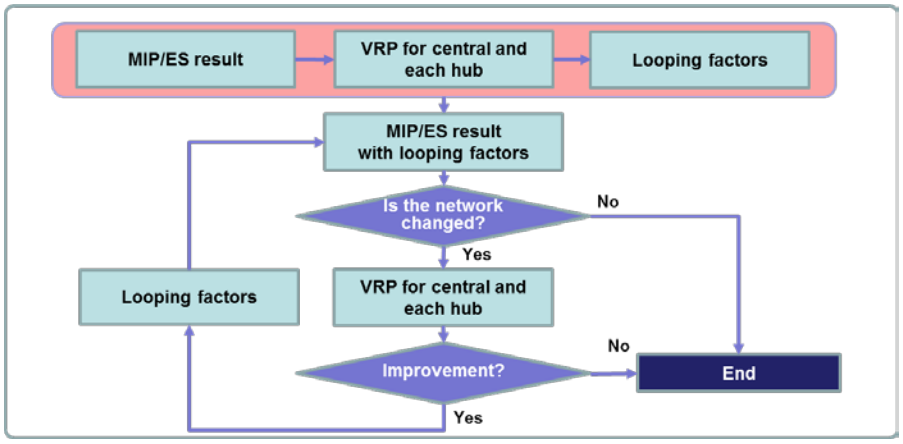


Figure 22. Apply looping factors

5.6.3 Vehicle routing problem

There are many algorithms that have been developed for the VRP. Because the VRP is known to be NP-Hard, many of these are heuristics. For this network problem, both an MIP formulation and a heuristic method are used in this research. Since we need to solve many VRPs while applying a looping factor, the MIP formulation is used for smaller problems where the VRPs can be solved efficiently, while the heuristic is used when the VRPs take too much time to solve optimally.

5.6.3.1 MIP Formulation

In this section, we describe a mathematical formulation corresponding to the VRPs that we solve. This formulation considers the vehicle type to use for each loop and its capacity. It uses a binary variable as a vehicle flow variable to show if there is travel between two locations using a specific vehicle.

Notation

$C_{ijt}^T, d_j, B_j, P_t^T, C, H,$ and T follow the same notation as the network MIP. Define

$x_{ijt} \in \{0,1\}$: 1 if i and j are connected using vehicle type t; 0 otherwise.

y_{ijt} : amount of vaccine transported from i to j using vehicle type t.

The following MIP is used to solve the VRP:

$$\text{Min} \sum_{t\in T} \sum_{i,j\in C\cup H} C_{ijt}^T x_{ijt} \tag{81}$$

subject to

$$\sum_{t\in T} \sum_{i\in C\cup H} x_{ijt} = 1 \qquad \text{for } \forall j \in H \tag{82}$$

$$\sum_{i\in C\cup H} x_{ipk} - \sum_{j\in C\cup H} x_{jpt} = 0 \qquad \text{for } \forall p \in H, \forall t \in T \tag{83}$$

$$\sum_{t\in T} \sum_{i\in C\cup H} y_{ijt} - \sum_{t\in T} \sum_{i\in C\cup H} y_{jit} = d_j \qquad \text{for } \forall j \in H \tag{84}$$

$$B_j x_{ijt} \le y_{ijt} \le P_t^T x_{ijk} \qquad \text{for } \forall i,j \in C\cup H, i \ne j, \forall t \in T \tag{85}$$

$$y_{ijt} \ge 0 \qquad \text{for } \forall i,j \in C\cup H, i \ne j, \forall t \in T \tag{86}$$

$$x_{ijt} \in \{0,1\} \qquad \text{for } \forall i,j \in C\cup H, i \ne j, \forall t \in T \tag{87}$$

Constraints (82) and (83) ensure that a facility is visited exactly once and that if a vehicle visits a location, it must also depart from it. Constraint (84) specifies that the difference between

the quantity of vaccines a vehicle carries before and after visiting a facility is equal to the demand of that facility. Constraint (85) ensures that the vehicle capacity is never exceeded.

5.6.3.2 Heuristic method

Our heuristic uses a constructive method based on the algorithm of Clark and Wright (1964). In this algorithm, point-to-point routes are combined to form a loop by choosing the routing path that gives the largest transportation cost savings at each iteration until every location is linked. For our network problem, vehicle type is considered when the savings on the route are calculated. For checking if a route is feasible, both vehicle capacity and trip distance are considered.

Modified Clark and Wright algorithm

Label the delivery locations as 1, 2, ..., *n* and label the origin as 0.

Determine the costs C_{ijt}^{T} to travel between all pairs of delivery locations and between each delivery location and the origin and for each vehicle type, i.e., for *i*=0, 1, .., *n*; *j*=0, ..., *n* and $j \neq i$, $t \in T$

1. Calculate the savings $S_{ijk}=C_{i0t}^{T} + C_{0jt}^{T} - C_{ijt}^{T}$ for all pairs of delivery -locations *i*, *j* and vehicle types *t* (*i*=1, 2...*n*; *j*=1, 2...*n*; $i \neq j$, $t \in T$).

2. Order the savings, S_{ijt}, from largest to smallest.

3. Starting with the largest savings, do the following:

(a) If linking delivery locations *i* and *j* results in a feasible route, then add this link to the route; if not, reject the link.

(b) Try the next savings in the list and repeat (a).

Checking for route feasibility

If the sum of vaccine volumes required at the delivery locations on the route is less than or equal to the capacity of the vehicle and the total travel distance of the vehicle is less than or equal to the maximum travel distance of the vehicle, the route is feasible; otherwise, the route is infeasible.

5.6.4 Numerical example

Table 47 shows results from the Cotonou province of Benin when vehicle routing is considered. This example is small enough that we can use the MIP to solve the network and also use an MIP formulation to solve the VRPs. The original optimal value for the network $\{N\}$ obtained after solving the problem is 142,543. The corresponding VRPs are then solved and the looping factor for the central distribution center to the hubs is computed as 0.4333 (i.e., 43.33%) while the looping factor for the hub to the clinics is 0.4585 (i.e., 45.85%). There is no hub to hub connection in this original network. The network cost with vehicle routing is estimated as Z=138,810; this is obtained by multiplying the transportation costs at each route (edge) by its looping factor. In particular, the transportation costs per km (C_{ijt}^{T}) from the central distribution center to each hub and from each hub to a clinic are multiplied by 0.4333 and 0.4585, respectively.

Next, the MIP is solved again with transportation costs based on the above looping factors and we obtain a new network $\{N_{new}\}$ with a cost of 138,393. After solving the associated VRPs this new network yields values of 1.00 and 0.391 respectively for the looping factors for central to hubs and hub to clinics each, and the true cost for this network $\{N_{new}\}$ with routing is estimated as $\underline{Z_{new}}$ =138,333. Since the network is changed and the cost has decreased

(138,333<138,810 (Table 47)), we perform a second iteration after resetting Z=138,333 and $\{N\}\equiv\{N_{new}\}$.

After the second iteration, the new network $\{N_{new}\}$ is different from $\{N\}$ and the VRPs yield new looping factors of 1.00 and 0.316. Since there is improvement in the network cost (Z_{new}= 137,494<138,333=Z (Table 47)), a third iteration is performed after resetting Z=137,494. After the third iteration, the solution to the network design problem is the same as the one from the previous iteration. Therefore, we stop here and accept this network structure with vehicle routing as the final one. Table 48 also shows the results for the same problem using the heuristic method for the VRPs instead of the MIP formulation. The iterations proceed in a similar fashion but the final network is different with looping factors of 1.00 and 0.3533 and a final cost of Z=137,831. The final network with the MIP VRP solver is little bit better than with the heuristic VRP solver (137,474 <137,831), because the MIP VRP solver provided optimal VRP solutions.

Table 47. Results of applying a looping factor for Benin (MIP-MIP)

		Initial Network	Iteration 1	Iteration 2	Iteration 3
MIP	Cost	142,543	138,393	138,171	137,494
Looping Factor (MIP)	C-H	43.33%	100.0%	100.0%	100.0%
	H-H	-	-	-	-
	H-I	45.85%	39.10%	31.60%	31.60%
	Cost (Z)	138,810	138,333	137,494	137,494

Table 48. Results of applying a looping factor for Benin (MIP-Heuristic)

		Initial Network	Iteration 1	Iteration 2	Iteration 3
MIP	Cost	142,543	138,753	138,419	137,831
Looping factor (Heuristic)	C-H	43.33%	100%	100%	100%
	H-H	-	-	-	-
	H-I	50.64%	41.85%	35.33%	35.33%
	Cost (Z)	139,106	138,539	137,831	137,831

Figure 23 shows the network structures at each iteration. As the iterations proceed, the number of hubs decreases. This is because allowing vehicle routing reduces the transportation cost substantially and this result is similar to the one obtained while conducting sensitivity analysis on transportation costs.

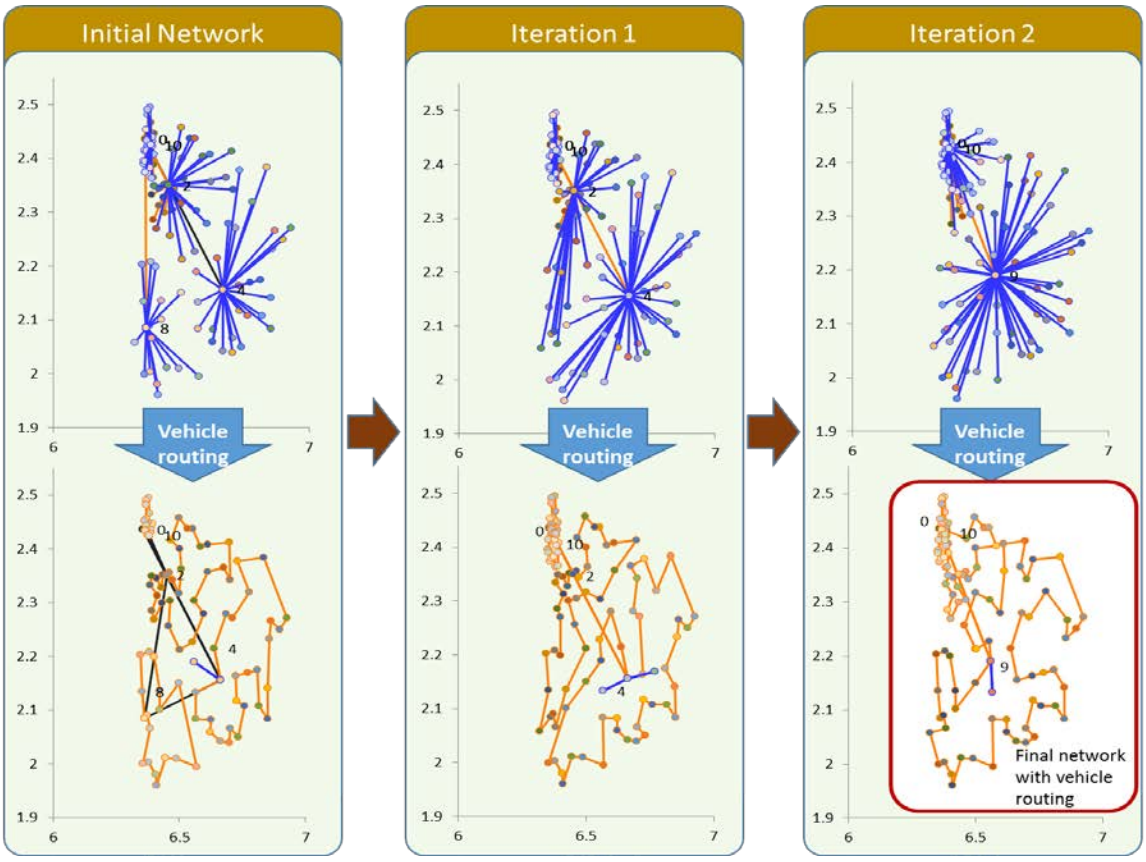


Figure 23. Network structure at each iteration (MIP-MIP)

5.6.5 Discussion

If a vehicle has enough capacity, visiting several locations during a trip is reasonable. Actually, this is common in practice. So solving a network assuming point-to-point trips can result in an undesirable solution. In this section, we described how vehicle routing can be incorporated into

the network problem using looping factors. Here, three looping factors – central distribution center to hubs, hub to hub, and hub to clinic - are used. This makes the simplifying assumption that the transportation costs between all points at one level and all destinations at the next lower level can be reduced by a similar percentage using delivery loops.

We cannot guarantee that the final network is optimal with vehicle routing because the network and the vehicle routing problems are not solved together. However, since vehicle routing has the effect of reducing transportation costs, if that reduced transportation cost can be incorporated when the network problem is solved, we can expect to find high quality solutions by applying looping factors.

5.7 IMPROVING THE EVOLUTIONARY STRATEGY

5.7.1 Introduction

The ES solves the network design problem from a central distribution center to hubs and a sub-network from hubs and clinics is automatically constructed by assigning the clinics to the nearest open hub. After the ES process, an MIP is used to optimize the sub-network. Since the sub-network is not optimized when the ES decides the best solution, the best ES solution before optimizing the sub-network might not be the best solution after optimizing the sub-network. For example, the 10^{th} ES solution can lead to the best solution of the network after optimizing the sub-network. In this section, we improve the ES for this problem by storing some of the solutions that are obtained during the intermediate ES iterations.

5.7.2 Improved ES

Since the ES is a stochastic optimization method, it is run for a predetermined number of replications in order to obtain the best solution. For example, if there are n replications of the ES, we have n ES runs and n MIP runs during post-processing. Without increasing the run time, we could possibly improve the ES results. Instead of solving an MIP corresponding to the best ES solution after each ES run and repeating this process n times, we start by storing the best n ES solutions from the first run. After each of the subsequent runs we update the list of the n best ES solutions found thus far by replacing existing solutions on the list with any better ES solutions found in the current run. After n replications of the ES, we solve n MIPs using the final list of the n best ES solutions. This method could possibly provide a network solution that might not have been possible to obtain using our original ES approach.

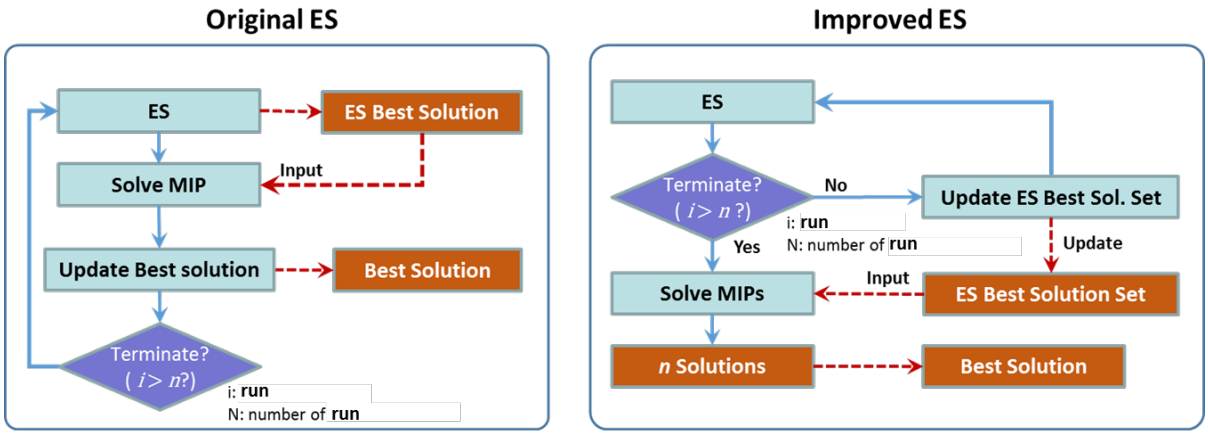


Figure 24. Original ES vs Improved ES

5.7.3 Numerical example

Table 49 shows the result of the original ES (left) and the improved ES (right) for 3 regions of Niger; 20 ES runs are performed for this network problem. The left half of the table (with the original ES) shows the best original ES value from each run and the value after applying the MIP to these. After 20 runs, the final best solution of the original problem yields a cost of 1,032,590. The right half of the table (with the improved ES) shows the final best 20 ES values (arranged in order) after 20 runs/replications. After using the MIP to further improve each, the best solution is 1,032,550 which is slightly better than the final solution of the original ES and could not be obtained by the original ES.

Table 49. Original ES vs improved ES for 3 regions of Niger

Run	Original ES	Original ES + MIP	Order	Improved ES	Improved ES + MIP	Rank (Improved ES + MIP)
1	1,038,580	1,035,840	1	1,035,330	1,032,590	2
2	1,040,200	1,036,690	2	1,035,860	1,033,120	5
3	1,035,330	1,032,590	3	1,035,870	1,033,130	6
4	1,036,130	1,033,390	4	1,035,940	1,034,710	15
5	1,036,440	1,033,700	5	1,035,950	1,034,710	15
6	1,036,290	1,032,720	6	1,036,070	1,032,550	1
7	1,036,670	1,033,930	7	1,036,290	1,032,720	3
8	1,035,330	1,032,590	8	1,036,330	1,033,590	9
9	1,036,330	1,033,590	9	1,036,350	1,035,120	18
10	1,035,330	1,032,590	10	1,036,360	1,033,200	8
11	1,037,110	1,033,540	11	1,036,400	1,033,690	10
12	1,037,840	1,034,270	12	1,036,440	1,033,700	11
13	1,036,440	1,033,700	13	1,036,470	1,035,230	19
14	1,035,330	1,032,590	14	1,036,470	1,035,230	19
15	1,036,670	1,033,930	15	1,036,590	1,033,050	4
16	1,038,580	1,035,840	16	1,036,670	1,033,930	12
17	1,036,660	1,033,920	17	1,036,810	1,033,160	7
18	1,037,470	1,033,900	18	1,036,850	1,034,110	13
19	1,036,330	1,033,590	19	1,036,870	1,034,130	14
20	1,036,290	1,032,720	20	1,036,900	1,034,830	17
Min	1,035,330	1,032,590	Min	1,035,330	1,032,550	
	Original ES				Improved ES	

Similarly, table 50 shows a comparison of the original ES and improved ES results for 4, 5, 6, and 7 (all) regions of Niger. The figures in the table are the final solution of each ES after processing via the MIP. In all cases, the improved ES results are slightly better than the original ES.

Table 50. Original ES vs. Improved ES results for Niger

	4 Regions	5 Regions	6 Regions	7 Regions
Original ES + MIP	1,304,170	1,647,660	1,761,630	1,904,160
Improved ES + MIP	1,302,930	1,647,570	1,759,320	1,902,850

5.7.4 Discussion

Here, the number of ES iterations and the number of solutions in the final set of the best ES solutions are the same, but this need not have to be the case depending on the problem size and time available to solve it. As the size of the problem increases, the list can be longer and cover more different network structures as long as the computational time does not increase too much. Also, the ES runs can be stopped earlier if we cannot update the ES best solution set for some predetermined number of experimental runs (replication). For example, we might start with a plan of n=50 runs, but if there is no improvement in the best ES solution set for 10 successive runs after the 17^{th} one, the ES process might then be halted after the 27^{th} iteration.

While the improved ES can generally provide a better solution, this is not necessarily guaranteed because the best solution obtained by the original ES method might not be included in the best n ES solutions after n ES runs. This issue can be readily resolved by also storing the

best solution from each ES run across the entire set of runs and also solving the MIPs corresponding to these after the completion of all runs. This requires at most n more MIP runs. However, since many of the best solutions from each ES run will be included in the ES best solution set, it is likely to be much smaller in practice. This additional step ensures that the improved ES is never worse than the original ES.

5.8 USING THE ES RESULTS AS MIP CONSTRAINTS

5.8.1 Introduction

For a large network problem, the rapid increase in computational effort makes the MIP an impractical approach. Because the network is fully connected, the MIP searches all possible solutions, and pruning the undesirable solutions is time consuming. If we can restrict the network structure by adding constraints that help decrease the solution space, the processing time can decrease. Since the improved ES generally provides very good solutions, one approach might be to make use of information about common characteristics of good solutions from the ES. In this section, we study what information from the best ES solutions we can use, and how.

5.8.2 Available network structure information from the ES solutions

The ES solutions provide the network structures from the central distribution warehouse to the hubs. The network structure from each of the solutions has the following information associated with it:

1. The number of open hubs
2. The number of hubs supplied by the central distribution center
3. The number of hubs supplying only clinics
4. Hubs that are open in all ES solutions in the solution set
5. Hubs that are closed in all ES solutions in the solution set
6. Hubs that are supplied by the central distribution center in all ES solutions in the solution set
7. Hubs that are not supplied by the central distribution center in all ES solutions in the solution set
8. Hubs that supply only clinics in all ES solutions in the solution set

Predetermining the number of hubs (based on 1, 2, and 3) can directly decrease the solution space in the MIP model. For example, if the number of open hubs is prespecified to be between four and six in a problem which has 11 potential hub locations, the MIP does not need to search among solutions that have more than six or fewer than four hubs. The information on hubs that are open or closed in all good solutions (based on 4 and 5) also can directly set the W variables in the MIP which represent whether a hub is open or not. Information on whether open hubs are supplied by the central distribution center or not (based on 6 and 7) can decide the value of the U variables from central distribution to hubs. Finally, the information on whether open hubs supply only clinics (from 8) sets the U variables. If a hub supplies only clinics, the values of U from the hub to other hubs becomes 0.

These can be categorized into three groups depending on where the information comes from. The first group (1, 4, and 5) is related to open hubs for each ES solution. The second group (2, 6, and 7) is connected to open hubs supplied by the central warehouse. The third group (3 and 8) relate to open hubs supplying only clinics.

Table 51 shows how to use the ES solutions for the first group. The example network has 10 candidate hubs and 10 ES solutions after the improved ES. The 0 or 1 in for each solution in the table represents whether the corresponding hub is open or not for that solutions. The last column is the total number of open hubs. The minimum number of open hubs is four (ES solution 1 and 3) and the maximum is six (ES solution 9). This implies that the optimal solution probably has four to six open hubs. So we can add following constraints into the MIP model.

$$\sum_{i=1}^{|H|} W_i \leq 6 \tag{88}$$

$$\sum_{i=1}^{|H|} W_i \geq 4 \tag{89}$$

The sum for each column is the number of times that the hub i corresponding to that column is chosen in our solutions. For example, the value of 10 for the second column indicates that the second hub is always selected as an open hub. The sum for the eighth column is 7 this indicates that the eighth hub is not always selected for opening. The first hub is never selected. If the sum for column i is 10, the i^{th} hub is always open hub and if the sum is 0, the hub is always closed. So we can add following constraints into the MIP model.

$$W_2 = W_3 = W_4 = 1 \tag{90}$$

$$W_1 = W_6 = W_7 = 0 \tag{91}$$

If we look at the eighth and ninth column, we can see that exactly one of these is selected in each of the 10 runs. So we could add the following constraint.

$$W_8 + W_9 = 1 \tag{92}$$

Table 51. First group example (whether a hub is open or not)

Solutions	Hub										No. of open hubs
	1	2	3	4	5	6	7	8	9	10	
1	0	1	1	1	0	0	0	0	1	0	4
2	0	1	1	1	0	0	0	1	0	1	5
3	0	1	1	1	0	0	0	1	0	0	4
4	0	1	1	1	1	0	0	1	0	0	5
5	0	1	1	1	1	0	0	0	1	0	5
6	0	1	1	1	0	0	0	1	0	1	5
7	0	1	1	1	0	0	0	0	1	1	5
8	0	1	1	1	1	0	0	1	0	0	5
9	0	1	1	1	1	0	0	1	0	1	6
10	0	1	1	1	0	0	0	1	0	1	5
Total	0	10	10	10	4	0	0	7	3	5	

Table 52 shows how to use the ES solutions for the second group. The example network is the same as with the first group. In this table, the figures represent whether a hub is supplied by the central distribution center (=1) or not (=0) for each ES solution. The last columns displays the number of hubs supplied by the central warehouse in each ES solution. The minimum number is two and the maximum is three. This indicates that the central warehouse probably supplies two to three hubs in the optimal network. So we can add following constraints into the MIP model.

$$\sum_{i=1}^{|H|} U_{0i} \leq 3 \tag{93}$$

$$\sum_{i=1}^{|H|} U_{0i} \geq 2 \tag{94}$$

The sum for each column is the number of times in our solution set that hub i is chosen to be supplied by the central warehouse. For example, the value of 10 for the second column indicates that the second hub is always supplied by the central warehouse. The sum for the third

column is 8, but the sum for the third column in Table 52 was 10. This implies that the third hub is not always supplied directly by the central warehouse when it is open. The fourth hub is never supplied by the central warehouse. If the sum for column i is 10, the i^{th} hub is always considered to be supplied by the central distribution center and if the sum is 0 even though the hub is open, it is supplied by some other hub. So we can add following constraints into the MIP model.

$$U_{02} = 1 \tag{95}$$

$$U_{04} = U_{05} = U_{0,10} = 0 \tag{96}$$

Table 52. Second group example (whether a hub is supplied by the central location)

ES Solutions	Hub										Total
	1	2	3	4	5	6	7	8	9	10	
1	0	1	1	0	0	0	0	0	1	0	3
2	0	1	1	0	0	0	0	1	0	0	3
3	0	1	1	0	0	0	0	0	0	0	2
4	0	1	1	0	0	0	0	0	0	0	2
5	0	1	0	0	0	0	0	0	1	0	2
6	0	1	1	0	0	0	0	1	0	0	3
7	0	1	1	0	0	0	0	0	1	0	3
8	0	1	1	0	0	0	0	1	0	0	3
9	0	1	1	0	0	0	0	1	0	0	3
10	0	1	0	0	0	0	0	1	0	0	2
Total	0	10	8	0	0	0	0	5	3	0	

Finally, Table 53 shows how to use the ES solutions for the third group. Once again, we use the same example as before. In this table, the figures represent whether a hub supplies other hubs or not for each ES solution (i.e., serves as a transshipment node for other hubs). We denote any hub that does not supply other hubs as a leaf hub. If the hub is a leaf hub, the value in the table is 1. If the hub supplies other hub(s) or is not open, the value is 0. The last column indicates

the number of leaf hubs for each ES solution. The minimum number is one and the maximum is three. This indicates that the number of leaf hubs is probably between one and three in the optimal network. Using just the current notation in the MIP model, it is impossible to express these additional restrictions. The sum for a column is the number of times across all the ES solutions that the corresponding hub i is chosen as a leaf hub. For example, the value of 10 for the fourth column indicates that the fourth hub is always a leaf hub. It can be seen that the entries for the fourth, fifth and tenth columns are identical to those in Table 53 for the same columns. This indicates that these two hubs serve as leaf hubs whenever they are chosen to be open. So we can add the following constraints into the MIP model.

$$\sum_{i=1}^{|H|} U_{4i} = \sum_{i=1}^{|H|} U_{5i} = \sum_{i=1}^{|H|} U_{10i} = 0 \tag{97}$$

Table 53. Third group example (whether a hub supplies other hubs)

ES Solutions	Hub										Total
	1	2	3	4	5	6	7	8	9	10	
1	0	0	0	1	0	0	0	0	0	0	1
2	0	0	0	1	0	0	0	0	0	1	2
3	0	0	0	1	0	0	0	1	0	0	2
4	0	0	0	1	1	0	0	1	0	0	3
5	0	0	1	1	1	0	0	0	0	0	3
6	0	0	0	1	0	0	0	0	0	1	2
7	0	0	0	1	0	0	0	0	0	1	2
8	0	0	0	1	1	0	0	0	0	0	2
9	0	0	0	1	1	0	0	0	0	1	3
10	0	0	1	1	0	0	0	0	0	1	3
Total	0	0	2	10	4	0	0	2	0	5	

5.8.3 Numerical example

Since the additional constraints from the ES results can reduce the search space for the MIP, we can expect a reduction in its run time. Table 54 shows results for subsets of Benin (Benin 1 and 2), with 20 runs of the ES. Benin 1 and 2 are smaller problems, so they can be solved by the MIP in reasonable time. In the table, "MIP" implies that the problem is solved by the MIP without any additional constraints. MIP + ES 1 means that the constraints from the first group are added into the problem. MIP + ES 1/2 means that the constraints from the first and second groups are added into the problem. When the Benin 1 problem is solved without any additional constraint, it takes 67 seconds. If we add the first group of constraints, the run time decreases to 30 seconds. When the first and second group constraints are added, the run time is only 8 sec. . For Benin 2, the results shows a similar performance improvement.

Table 54. Run time for Benin 1 and 2

Region	No. of Locations	MIP	MIP + ES 1	MIP + ES 1/2
Benin 1	128	67 sec.	30 sec.	8 sec.
Benin 2	162	153 sec.	88 sec.	13 sec.

Table 53 shows another example of a larger subset of Benin (Benin 3). This example is with two regions of Benin (Cotonou and Porto Novo) with 271 locations. The original MIP cannot be solved for this problem. After 30 runs of the improved ES, the cost of the best solution is 264,949 with a 2,940 second run time. When we use only the first group information, the MIP still cannot be solved even after running for 24 hours. When the second group information is also used, we can solve the problem in 318 seconds with a value of 264,802, which is slightly better

than the ES solution. This example shows that adding constraints mined from the ES result can lead to better solutions from the MIP formulation.

Table 55. Results for Benin 3

Benin 3	Improved ES (30 runs)	MIP + ES 1	MIP + ES 1/2
Best Solution	264,949	264,802	264,802
Run time	2,940 sec.	Stopped after 24hours	318 sec.

The next example is for two and three regions of Niger and the results are shown in Table 56. The Niger two-region instance is the largest problem for which we were able to obtain an optimal solution with the original MIP formulation albeit in 196 hours of run time. This example shows how much of a reduction in run time of the MIP can be obtained by using the ES results. Note that MIP+ ES 1/2/3 means that constraints from all the groups are added into MIP. Without additional constraints, it takes 196 hours to get the optimal solution. However, as we add more constraints, the run time decreases to 61.8 hours, then to 11.5 hours and finally, to 0.5 hours with all three constraint groups. Thus we are able to solve the same problem using only 0.3% of the original MIP run time when all information from the ES solutions is used. The Niger 3 region instance could not be solved at all by the original MIP. Even when the constraints from the first and second group are added, we are still unable to obtain a solution. But, when constraints derived from all three groups are inserted, the MIP could be solved in 16.4 hours.

Table 56. Results for two and three regions of Niger

Niger		MIP	MIP + ES 1	MIP + ES 1/2	MIP + ES 1/2/3
2 Regions	Best Solution	605,190	605,190	605,190	605,190
	Run time	196 hours	62 hours	11.5hours	0.5 hours
3 Regions	Best Solution	1,032,593	1,032,593	1,032,593	1,032,551
	Run time	Stopped after 48 hours	Stopped after 24 hours	Stopped after 24 hours	16.4 hours

5.8.4 Discussion

Clearly, adding constraints derived from the ES solutions into the MIP model can significantly reduce the run time because it decreases the search space; note that this search space still includes the best solution from the ES results. There are two issues when we use the ES solutions. First, the number of ES solutions to use should be decided carefully. If we have too many, the search space might not be reduced sufficiently to save run time because the ES solution set might include some relatively poor solutions that lead to relatively weak constraints. For example, as we have more ES solutions, the range of the number of open hubs will increase or the open hubs that are always selected might not be found. Conversely, if we do not have enough ES solutions, the solution space might be too tight for the MIP with the additional constraints in order to be able to find a better solution. There could also be correlations that are coincidental. For example, in Table 21, the eighth and ninth hubs are mutually exclusive in the 10 ES solutions, so the constraint $W_8 + W_9 = 1$ might be added. But this might be a coincidence, and it might not be easy to say whether these hubs are truly mutually exclusive; we should probably look at the geographical relationship between two locations before using this constraint. Even if hub A and hub B are chosen to be mutually exclusive, if they are located far apart, it is probably better not to use this constraint.

Finally, we also experimented briefly with constraining the number of levels in the network. In the examples of Benin in section 5.8.3, we can observe that the depth of the optimal network might be two since all the open hubs are supplied by the central distribution center in all ES solutions. Therefore, we could also try limiting the depth of the network. The constraint restricting the network depth to two is obtained by not allowing a flow between candidate hubs: $U_{ij} = 0$ for all $i, j \in H$. If we add this constraint for Benin 1, 2, and 3 examples, the run times

are 28, 58 and 1,528 seconds. These run times are shorter than MIP + ES 1 but longer than MIP + ES 2/3. This is likely because ES 2/3 constraints already involve depth restriction constraints and appear to be more efficient than adding the depth constraint.

5.9 DISCUSSION AND CONCLUSIONS

Cordeau et al. argue that solving a real-life problem to optimality is rarely justified due to errors contained in the data estimates. Since the margin of error for data tends to be larger than 1%, they suggest that it is adequate to run the mathematical solver until a feasible solution within 1% of optimality has been identified (Cordeau, Pasin, & Solomon, 2006). In the vaccine network, the demands at local clinics, transportation costs, and storage costs are fluid and we use estimated/averaged values here for these here. The solutions produced by the ES are reasonably close to the optimal MIP solutions (less than 1% difference). In addition, the computation time is vastly smaller. Therefore, solving the vaccine distribution network design problem using an ES approach can be a good way to address the problem.

This chapter focuses on designing a vaccine distribution network in terms of cost minimization. Obviously, the resulting network is more cost effective than the original one. However, there are other considerations that are not able captured by this model. First, we may have to consider the cost of closing a hub. This is not considered in our model since usually the candidate hub is a local health facility with other functions that it will continue with, even without the vaccine distribution role. But if a hub is not open, the devices used in the hub, such as refrigerators, might be moved to another facility that needs them. So, if the cost associated with this is included in the model, we can have more precise results. Second, the new network

usually has fewer intermediate hubs. This might increase the risk of losing more vaccines due to unexpected circumstances such as unstable power supply. The countries supported by the WHO-EPI program still have problems such as unannounced electricity blackouts and poorly trained workers, and a significant number of vaccine vials might be wasted because of undesirable handling of vaccine or events such as electricity loss. The fewer the number of facilities where vaccines are stored, the more the amount of vaccines at any single facility and the higher the consequences of such losses. Third, vehicles with limited capacity are used in the model. But in practice, they can transport more vaccines, especially at the clinic level. As an extreme example, when a vehicle has a capacity of 5 liters and 5.1 liters of vaccine should be delivered, a vehicle may be able to carry 5.1 liter of vaccine in a trip, but we assume in our model that two vehicle trips are needed.

This chapter also does not consider the introduction of new vaccines in the future. If a new vaccine is introduced, it will require more space in storage and transportation and may change the optimal network structure. In order to address this, some kind of robustness analysis with respect to the vaccine schedule should be performed. This can be done as follows. First, set the demands at clinics based on different vaccine schedules. Second, obtain the vaccine networks for each scenario. Third, compare the cost of each network for the different demands. The network which has the lowest total cost for all demands could then be the final network

For NP-hard problems like the one in this chapter, the MIP computation time increases dramatically as the problem size gets larger. Since most real world vaccine distribution networks have many candidate hubs and demand nodes, finding the optimal solution using an MIP formulation of the problem cannot be done in a reasonable amount of time. Therefore, in this chapter, an ES algorithm is proposed to solve this problem, and it is shown that the ES

consistently produces a near-optimal solution in reasonable times. In addition, visiting several locations during a trip is common practice. In order to model this, the two step procedure using looping factors was introduced. Since the effect of vehicle routing is a reduction in transportation costs, solving the network problem after modifying the transportation cost using a looping factor presents a comparable result with solving the network problem using vehicle routing. Therefore, this study can help decision makers who plan to redesign their distribution chain which has features similar to those described here.

6.0 SUMMARY AND CONCLUSIONS

In this dissertation, we have proposed models and methodologies that can help increase the efficiency of the WHO-EPI vaccine supply chain in meeting the demand for life-saving vaccines in low and middle income countries. Despite many technological advances that have been made over the last four decades, these distribution chains and their operations still pose many problems in many places around the world. The problems relate both to how the distribution chain is designed as well as to how it is operated, and in this dissertation we address both of these aspects. The overall goal is to improve coverage and to be able to inoculate the millions of children who still do not receive life-saving vaccines against preventable diseases because of inadequacies in the distribution system.

This research had focused on three major areas. First, we have introduced four optimization models for the vaccine outreach supply chain in developing countries. Since the level of coverage that one gets from outreach in practice is not clearly understood, we develop three different models, each of which is based on a different plausible coverage assumption, and we have presented robust approaches to cope with the uncertainty associated with our coverage assumptions, as well as the uncertainty associated with demand for outreach. To our knowledge the work reported here is the first to provide a formal modeling framework for decision making with respect to outreach. Currently, there are no standard guidelines for outreach, and these

models can aid decision makers to improve coverage when they are establishing outreach policies.

In next two chapters, we have addressed operational issues and focused on simplifying vaccine ordering logistics. This is important because in many low and middle income countries these operations are performed in the field by personnel who are not necessarily trained for logistics activities. Thus it is critical to develop operational procedures that are efficient but also simple enough to be implemented in a resource constrained environment. First, we have suggested a modular packaging system for vaccines. The modular packaging can be obtained by standardizing the dimensions of vaccine vials and packaging units as far as possible. This could offer significant advantages over a conventional vaccine packaging system with respect to space efficiency as well as convenience of handling vaccine orders by allowing for more vaccines to be stored within the same volume in the storage devices. Second, we have proposed vaccine ordering policies using inner packs for the clinic level in order to simplify how inventories are managed in the field. The proposed policies can reduce errors in counting and ordering, as well as order fulfillment effort, and are based on lean concepts that are already used widely in manufacturing. Because these policies might need a larger packaging unit that increases the required storage volume, we have performed the required analyses with respect to cold storage during transportation as well as at clinics in order to evaluate their impact. The proposed simplified ordering policies are shown to work better when the vaccine inner packs are standardized because the modular packaging can use space more efficiently.

Lastly, we address the fundamental issue of designing the vaccine distribution network based on the specific characteristics and operating environment of the country where it will be implemented. This is similar to how any other supply chain network is designed and in contrast

to the somewhat rigid structure that exiting WHO-EPI networks have. We have presented methodologies which can improve the design of vaccine distribution networks at a country level while considering constraints on capacity for storage and transportation, by formulating the problem as a mixed integer program and developing an evolutionary strategy that can be used in conjunction with the MIP. Computational examples based on real data are used to illustrate that this is an appropriate approach. In order to reflect how deliveries might be made in practice, we have developed the notion of looping factors and presented how these can be applied in the network problem. In addition, we have suggested ways to improve the efficiency of the ES algorithm without any significant additional computational effort.

Although we have addressed a diverse set of issues in this research there are still open questions including the design and optimization of alternative outreach policies that can be standardized in the field, the development of easy-to-use policies and procedures that can reduce operational inefficiencies (especially at the clinic level), and the development of better and more detailed models for designing/redesigning the WHO-EPI network that can also be solved efficiently.

There is also the potential to evaluate different modeling frameworks because the current MIP is a flow based formulation and its computational time grows quickly as the size of the problem gets larger. Alternative formulations may be able to reduce the computational time. All of these present areas for future research.

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