MODELING THE WHO-EPI VACCINE SUPPLY CHAIN IN LOW AND MIDDLE INCOME COUNTRIES

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The enormous economic impact of diseases has drawn global attention and controlling diseases through a vaccination program is one of the highest priorities in healthcare decision making. However, successful implementation of vaccination programs must also consider distribution network design and logistical feasibility. In this research we address this issue via three broad contributions. First, we develop a generic mathematical programming model of the WHO-EPI vaccine distribution network in low and middle countries, and adapt the model to answer actual vaccine logistics questions such as assessing the feasibility of new vaccine introductions, changing the distribution network design, and changing the vial size of an existing vaccine using the West African country of Niger to illustrate this. Second, we explore integrating vaccine distribution decisions with immunization policies by developing a framework for linking the vaccine supply chain model with a disease propagation model. The framework is used to assess measles interventions in Niger in order to help policy makers decide on an appropriate vaccination policy. Third, we address the significant challenge of increasing the clinic visit rate, especially in areas with limited health care resources and high-risk populations. To do this we explore the application of passive cold devices for vaccine delivery at remote vaccination sites. Such mobile devices are easy to deploy at locations that are off the electricity grid or have an

unstable energy supply, and they can also be used to support outreach vaccinations to families in rural areas. We develop a computational model to evaluate the cost effectiveness of different device designs for vaccine delivery in real world distribution networks. We also conduct sensitivity analysis to determine which design is most robust with respect to fluctuations in cost performance.

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1.0 INTRODUCTION

1.1 MOTIVATION

Issues with Vaccine Delivery

Infectious diseases kill millions of people every year (Mortality data, 2010). In addition, the enormous economic impact of diseases has drawn global attention. Controlling epidemics is one of the highest priorities in public health decision making. A large amount of resources are allocated to immunization programs, which include a variety of interventions for disease prevention and treatment. One of the most effective ways to do this is vaccination, which helps populations that are likely to be infected develop immunity to diseases.

The introduction of vaccines has significantly improved the quality of life and extended life expectancy in many parts of the world. By taking advantage of technology, vaccines today are produced less expensively and more quickly. However, vaccine shortages are still a major issue in low income countries, where limited resources are available for immunization programs (Matthias, D. M., et al., 2007). Because vaccines are often not effectively delivered to meet the requirements, people are still afflicted with infectious diseases. In addition, poor vaccine supply chains often result in wastage of vaccines during distribution (Setia, S., et al., 2002).

Most vaccines need to be stored in a temperature controlled environment (either in a freezer or a refrigerator) all the time; improper storage temperatures reduce vaccine potency and result in recipients not being protected against diseases (Adu, F. D., et al., 1996) (Lala, M. K.

and Lala, K. R., 2003) (Hanjeet, K., et al., 1996). Therefore, appropriate cold storage equipment is an essential prerequisite in order to ensure the quality of vaccines administered to the population.

The challenges of operating an effective vaccine supply chain motivate study of the issues that relate to vaccine distribution in order to help improve resource utilization and to mitigate disease transmission. Specifically, these include the following:

Vaccination Activity

Vaccination activities include routine immunization (RI) and supplemental immunization activity (SIA). RI occurs at clinics or health offices where vaccines are administered to children according to a pre-specified immunization schedule, based on the World Health Organization guidelines and the Expanded Program on Immunization (EPI) (Expanded Program on Immunization (EPI), Retrieved 2011). In general, the coverage age groups for RI range from birth to five years of age.

SIA is implemented to supplement RI by providing recipients a second chance to develop immunity against diseases. SIA is also implemented in the form of targeted campaigns when there are outbreaks of diseases. The priority areas and target populations are determined based on estimates of future disease prevalence. To obtain high coverage, vaccination can take place at any location and is not limited to clinics. Health workers often carry vaccines down to villages or schools during vaccination days. Intensive vaccination outreach programs can often cover even the most remote areas where health care resources are insufficient. SIA reduces vaccine wastage because demand is aggregated (Lee, B. Y., et al., 2010). However, to provide unusually large amounts of vaccines in a short time period is a major challenge in vaccines logistics.

Vaccine Supply Chain

Distributing vaccine from manufacturers to the final recipients is composed of a series of procurement, storage, shipment and other related activities. One of the challenges is that vaccine demand and supply are variable. In many low and middle income countries, the demand for vaccines is increasing exponentially because of the continued growth in the birth rate. Additionally, vaccines are also used for the purpose of immediate response to disease outbreaks. Large quantities of vaccines are often stocked for mass vaccinations to prevent disease (Zimbabwe measles immunization and child health days campaign, 2010). In most low-income countries, vaccines are supplied by international organizations, and can come from multiple sources. It is difficult to coordinate orders from different suppliers. Furthermore, information provided to vaccine manufacturers can often be unreliable. The lack of good data leads to inaccurate demand forecasts, which is a critical impediment to proper planning.

It is also important to recognize that vaccine distribution considers both equity and efficiency. The goal is to provide vaccines uniformly to everyone in the system, while also ensuring that infections can be averted as much as possible. To account for the trade-off between equity and efficiency, it is important to balance coverage within an optimal vaccine system design.

This dissertation presents mathematical models of the vaccine supply chain. While the emphasis is on developing a general model that can be widely applied, Niger is used as an example for illustrating vaccine supply chains in practice. In Niger, vaccines are provided by UNICEF via twice-a-year shipments to a central depot in the city of Niamey. Vaccines are then

pushed down to eight regional warehouses once every three months, and 42 district warehouses pull vaccines from the regional warehouses on an approximately monthly basis. Similarly, 695 clinics pull vaccines from the district warehouses about once every month. The entire supply chain includes a total of 746 locations, where each is equipped with different volumes of cold capacity for holding inventory; however, not all of the clinics/warehouses are currently operational. Shipments are made by using either a cold truck (one with refrigeration capabilities) or a regular truck. Cold boxes or cold carriers are required when vaccines are delivered by regular trucks.

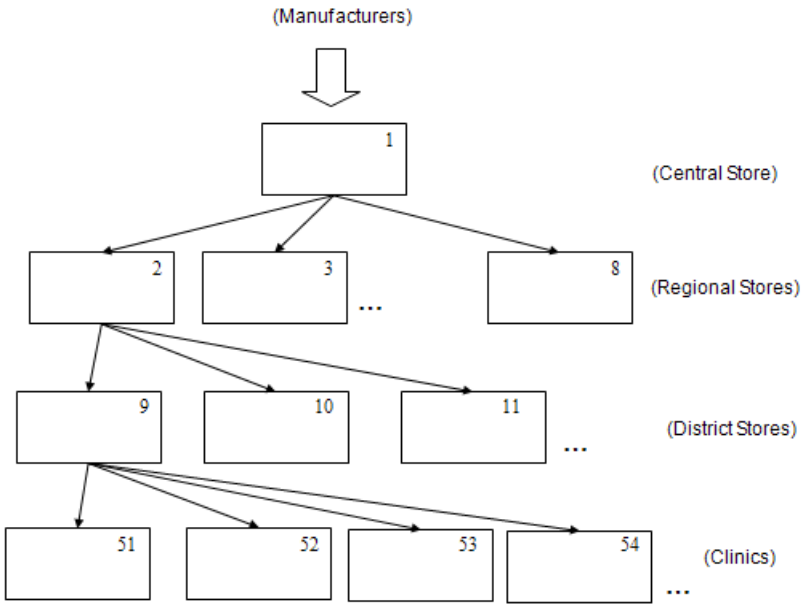

Figure 1. Niger vaccine supply chain

Based upon 2011 statistics, the total population of Niger is about 16 million, with most people living in the southern regions (The world factbook : Niger, 2012). The northern regions

are inhabited by nomadic people who migrate to areas where there is food available for their animals. The population distribution is unbalanced and changes seasonally. Niger also has a very large population of children; around 50% of the population is under 14 years of age. Vaccinations occur at clinics that are open four days per week, with patients generally getting vaccines at the closest clinic.

Modeling of Infectious Diseases

Infection occurs when the agent of disease enters into a host. Agents include viruses and bacteria; the host focused on in this research is humans. Diseases are spread in populations through several different modes of transmission, including food, physical contact, and blood borne, airborne and waterborne contacts, depending on the pathogens of diseases (Burt, 1998). The symptoms that result from an infection are different, and some diseases do not cause illness in a host, while in other cases disease can be transmitted to other hosts regardless of the health of infected individuals. Infectious disease remains a leading cause of death in low and middle income countries; on average, 60% of deaths in African countries are due to infectious diseases (World health statistics, 2008). Some infectious diseases, such as HIV and flu, have emerged in both developed and developing countries.

Modeling diseases transmitted in populations requires a conceptual framework to estimate the spread and prevention of disease. This provides an opportunity for policy makers to prepare for the disease outbreak, as well as to make immunization decisions. A variety of approaches can model the mechanism of the transmission process, and people use these models to investigate disease propagation in a population (Long, E. F. and Brandeau, M. L., 2009). One of the approaches related to this study is compartment modeling. Populations are divided into

different compartments, such as *susceptible*, *infected* and *recovered*, and there is a transition between two compartments according to some a specified rate. The first compartment model was developed by Kermack and McKendrick in 1927 (Kermack W. O. and McKendrick A. G., 1927). They presented a nonlinear system to characterize an epidemic in a population by the numbers of individuals in each compartment over time. The model can predict the prevalence of a disease by solving the equations representing the system.

1.2 RESEARCH OBJECTIVE

Our research objective is to develop systems that can address the issues related to vaccine supply chains in order to help implement immunization programs in low and middle income countries. We study three separate topics in support of this objective. First, from a vaccine logistics perspective, we examine vaccine availability, given a set of constraints that correspond to the supply chain limits. Second, from a disease control perspective, we estimate disease propagation based on available vaccines given to populations of different age groups. It should be noted that vaccine availabilities in turn, are impacted by the supply chain and the fact that poor storage conditions might exist at the vaccination locations. Finally, we explore various passive cold device designs to improve vaccine availability and store vaccines in a proper temperature range during the vaccination periods. These topics are combined with real data for answering questions in which policy makers are interested. The integration paves the way to assess a wide variety of decisions for controlling epidemics and helps implement disease prevention programs in low and middle income countries.

1.3 CONTRIBUTIONS

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

- Creation of a mixed integer linear programming model for vaccine supply chain modeling (VMIP) that uses the C++ computer language to construct the constraints, and then solves the problems modeled using CPLEX (IBM Corporation).
- Incorporation of real world information into the model to assist decision makers in developing vaccine policies that use an operations research approach to answer relevant policy questions.
- Use of the model to analyze the impacts of new vaccine introductions on existing cold chain systems in low and middle income countries, and to help policy makers make appropriate adjustments to minimize problems arising from new vaccine introductions.
- Identification of bottlenecks in the supply chain and optimal capacity expansion strategies for different scenarios. The information can be used in conjunction with immunization programs to prepare for a comprehensive plan of allocating resources to where they are most needed.

- The model can assess how vaccine availability is affected by changes to the current network structure. These network changes can be evaluated to help design makers assess different network structures and choose the best alternative to meet the immunization needs of their country.
- Exploration of a stochastic model of disease transmission in multiple communities and development of a linkage between the disease and supply chain models to prepare for vaccination strategies.
- Application of the linking to assess vaccination strategy effectiveness using the metric of infections averted and to identify resources needed.
- Investigation of passive cold device designs for various use cases to determine which designs are most cost effective.
- Robust analyses to assess the interactions between passive cold device designs and supply chain policies.

2.0 PRELIMINARIES

There is a large body of literature that is related to the proposed research and it falls into three broad categories: supply chain management, vaccine supply chains, and disease modeling. Each of these is now described in more detail.

2.1 SUPPLY CHAIN MANAGEMENT

A supply chain depicts the flows of merchandise and information from suppliers to customers. There are many components or links in a supply chain including suppliers, manufacturers, distributors, retailers and customers (Chopra, S. and Meindl, P., 2004) (Simchi-Levi D., et al., 1999). The structures of most supply chains can be represented as networks where the entire system involves a variety of stages and each stage consists of multiple facilities. Each node represents a function on the network and different nodes use different enterprise management disciplines.

The objective of supply chain management (SCM) is to maximize the overall value of the entire supply and distribution system (Chopra, S. and Meindl, P., 2004). Products are manufactured and distributed in the right quantities, to the right locations at the right time, in order to satisfy demand at minimum cost. In the last few decades, numerous studies have been published that cover a broad spectrum of SCM problems. Reviews and surveys of the SCM domain can be found in (Burgess K., et al., 2006) (Fawcett, S. E., et al., 2008) (Giunipero, L. C., et al., 2008) (Jain J., et al., 2010) (Meixell, M. J. and Gargeya, V. B., 2005) (Power, 2005)

(Storey, J., et al., 2006). More recently, Fawcett et al. (2008) provide a quantitative and qualitative analysis of the benefits, barriers, and bridges to successful collaboration in strategic supply chains (Fawcett, S. E., et al., 2008). Manuj and Mentzer (2008) propose risk management strategies in global supply chains to enhance sustainable competitiveness by reducing costs without compromising customer satisfaction (Manuj I. and Mentzer J. T., 2008). There are many facets of SCM research but these can be broadly classified into three categories (Chopra, S. and Meindl, P., 2004).

Supply chain design which deals with decisions that have a long-term effect. The structure of the supply chain is decided at this phase including the number and size or capacity of facilities and a general plan for how materials will flow through the supply network.

Supply chain planning which includes decisions that are updated a few times per year such as production planning, inventory policies and transport strategies.

Supply chain operation which considers the weekly or daily time frame. Example decision problems include scheduling, vehicle routing and setting triggers for placing replenishment orders.

This research focuses on supply chain design and supply chain planning issues related to vaccine delivery for low-income countries. Possible policy decisions include how best to allocate vaccines for disease prevention, cold capacity expansion for vaccine storage, determining the best vaccine shipping frequency from warehouses to clinics and deploying cold equipment for vaccine storage at remote sites. These and other vaccine supply chain policy decisions are discussed in more detail in later sections.

2.2 VACCINE SUPPLY CHAINS

Traditional supply chain models consider issues such as capacity analysis, inventory positioning, procurement, production, routing and transportation modes (Melo, M. T., et al., 2009). In vaccine supply chains, there are several additional characteristics that make the modeling and analysis more complicated:

- Temperature requirements for vaccines during transport and storage. In particular, the need for an effective cold chain to maintain vaccine efficacy.
- Difficulties due to the potential for open vial waste. For many vaccines any doses left over from an open vial must be discarded at the end of a vaccination session.
- There are multiple vaccine types in the set (or regimen) of vaccines that a child must receive.
- Vaccines have a limited shelf life.
- Vaccine demand can be steady (routine birth and child dosing schedules) or there may be campaigns designed to immunize for a specific vaccine or set of vaccines during a short period of time.
- There can be significant variability in the supply of vaccines from international donations.

To address these system characteristics it is necessary to utilize knowledge and resources from several different fields of research including operations research, logistics, public health, and public policy. We now review the existing literature specifically related to vaccine supply chain problems. The literature is organized into the three general categories of vaccine distribution, vaccine manufacturing, and vaccine policy.

Vaccine Distribution

Several authors have explored the issues of modeling vaccine distribution in a supply chain context. Many of these use mathematical programming to formulate typical problems. Early work in this area includes Longini et al. (Longini, I. M., et al., 1978). They present a deterministic model to select the optimal influenza vaccine distribution pattern among multiple age groups in a "standardized American community" when a limited quantity of vaccine is available. The model specifies heterogeneous mixing patterns among individuals in different age groups and a vaccine distribution plan can then be determined for each subgroup population to minimize the likelihood of epidemics. Kaplan et al. use a mathematical model to evaluate various strategies for mitigating the impact of a smallpox bioterrorist attack in a large U.S. city by providing vaccines to the various subgroup populations prior to the attack (Kaplan, E. H., et al., 2002). Kaplan and Merson investigate allocating federal HIV-prevention resources (Kaplan, E. H. and Merson, M. H., 2002) and propose a balanced policy that promotes both equity and efficiency. Ferguson et al. address the importance of using mathematical models to assess the potential for smallpox outbreaks due to bioterrorist attacks (Ferguson, N. M., et al., 2003). They show the use of models in planning for disease control by contrasting various prevention policies. Andrew and Longini determine minimal vaccine allocations to prevent epidemics (Andrew, N. H. and Longini, I. M., 2003). They find the threshold of vaccine coverage by

solving for the critical vaccination fraction that could reduce the disease reproduction number to a value less than one. Earnshaw and Hick use a linear programming model to make decisions concerning the allocation of HIV prevention resources. The objective is to maximize the number of HIV transmission infections averted (Earnshaw, S. R. and Hicks, K. A., 2007). The potential number of infections that may be averted is calculated by using epidemic models. Then decisions are made to allocate available funds to priority subpopulations in different geographic regions for HIV prevention.

Vaccine Manufacturing

Chick et al. study shared contracts that offer incentives to both vaccine manufacturers and governments (Chick, S. E., et al., 2008). Given a vaccine demand provided by the government, the manufacturer decides how much vaccine to produce. The decision is based on optimizing the performance of the supply chain insuring that sufficient influenza vaccines are supplied. Jacobson et al. use a stochastic model to assess the probability of stock-out for different vaccine stockpile levels (Jacobson, S. H., et al., 2006). The paper also considers the impact of manufacturing disruptions that can interrupt supply. They suggest using vaccine stock levels that ensure that demand is satisfied while considering potential future production interruptions.

Vaccine manufacturers also have to make decisions about what multi-dose vial sizes to manufacture. In practice, a large amount of vaccine doses are wasted because for some vaccine types all vaccine vials open at the end of a vaccinations session must be discarded. Thus, larger multi-dose vials may induce more open vial waste if patient demand for the particular vaccine is relatively low during a vaccination session. Lee et al. conduct a cost analysis to determine the most cost effective vial size to use for different demand values (Lee, B. Y., et al., 2010). These

results can help policy makers decide which vial size to order and can help vaccine manufacturers determine which vials sizes may be best to produce based on user needs.

Vaccine Policy

Jacobson et al. use an integer programming model to optimize the procurement of children's immunization vaccines (Jacobson, S. H., et al., 1999). They consider vaccine costs, injection costs and clinic visit costs. The objective is to minimize the total cost for fully immunizing a child. More recently, Lee et al. develop a mathematical model to represent the vaccine supply chain in a country (Lee, B. Y., et al., 2012). They use the model to access the impacts of introducing Pneumococcal and Rotavirus vaccines into the Routine Immunization Program in Niger. Lee et al. use a discrete event simulation model of Thailand's vaccine supply chain to analyze the effect of replacing a ten-dose vaccine vial with a single-dose vial (Lee, B. Y., et al., 2011). The simulation results show that switching to the single-dose vaccine presentation reduces open vial waste but increases disposal and administration cost.

One important point to note is that other than the recent work by Lee et al., virtually all of these models apply to the developed world and do not address the WHO-EPI chain in lower and middle income countries (LMC).

2.3 DISEASE MODELING

The widespread use of vaccinations has greatly reduced infectious disease incidence worldwide (Expanded Program on Immunization, 2011). However, the vaccine coverage rates required to

greatly reduce or eliminate certain diseases in many low-income countries are still not being attained. Decision-makers continue to face challenges in determining how to utilize supply chain resources in order to raise vaccine coverage rates.

To evaluate the effectiveness of an immunization program, credible projections of future disease propagation under various possible vaccination strategies are needed. These projections can be obtained using disease models (Hethcote, H. W., 2000). These mathematical models are used to study transmission mechanisms and can thereby assess the impacts of using different vaccination strategies. Mathematical models can also determine the herd immunity threshold (the minimum coverage level needed to control a disease) which can then be used to establish target levels of vaccine coverage. Therefore, analysis via mathematical models provides valuable insights for planning vaccination programs (Ferguson, et al., 2003).

One of the earliest references to a mathematical disease propagation model is Reed and Frost in the 1920s. They first used individual-based models to track the behavior of disease propagation in a population. The probability that a susceptible individual will be infected during time period t (λ_t) is determined by the following equation:

$$\lambda_t = 1 - (1 - p)^{I_t}$$

where p is the probability of an individual having an effective contact (a contact that transmits the disease) in a time period, and I_t is the number of infected individuals in period t.

Kermack and McKendrick published the classical SIR compartment model in 1927 (Kermack W. O. and McKendrick A. G., 1927). Given that disease outbreaks begin with an infected individual (index case), susceptible individuals may become infected if they come in contact with an infected individual. Basic versions of the SIR model do not construct a separate

compartment for those individuals in the latent period (individuals are infected but not yet infectious) but rather assume that once an individual is infectious, that person can transmit the disease to other susceptible people. After completing the infectious period, infected individuals enter a recovered state. Basic SIR models assume all recovered individuals develop permanent immunity and cannot be infected again. A basic SIR model is now illustrated with a numerical example (Anderson, R. M. and May, R. M., 1991). All individuals move through the following states:

$$[Susceptible] \rightarrow [Infected] \rightarrow [Recovered]$$

Consider a closed population (i.e., there are no births, deaths or migration) with an initial distribution as shown below:

$$\begin{bmatrix} Susceptible \\ Infected \\ Recovered \end{bmatrix} = \begin{bmatrix} 100 \\ 1 \\ 0 \end{bmatrix}$$

If the disease spreads through person to person contact with a *basic reproduction number* (R_0) equal to 2 then each single infected individual can cause at most two secondary cases. Note that the rate at which one infected individual generates new infections declines as the number of susceptible individuals is depleted. The distribution of infection states in successive steps will be the following:

$$\begin{bmatrix} 100 \\ 1 \\ 0 \end{bmatrix} \rightarrow \begin{bmatrix} 98 \\ 2 \\ 1 \end{bmatrix} \rightarrow \begin{bmatrix} 94 \\ 4 \\ 3 \end{bmatrix} \rightarrow \cdots$$

In the vectors above, the number of new infections at each step is calculated based on the number of infected individuals, basic reproduction number and proportion of susceptible individuals using the following relationship:

$$Infected\ individuals \times R_0 \times \frac{Susceptible\ individuals}{Total\ Population}$$

The number of new infections demonstrates exponential growth in the early stage of an outbreak. After most of the susceptible individuals have been infected (so they are infected or recovered), the number of new infections starts to decline. In the end, the system will reach equilibrium and the numbers of individuals with each compartment remains unchanged over time. In the case of a closed population the number of new infections will eventually fall to zero but in an open system it will stabilize to a constant value.

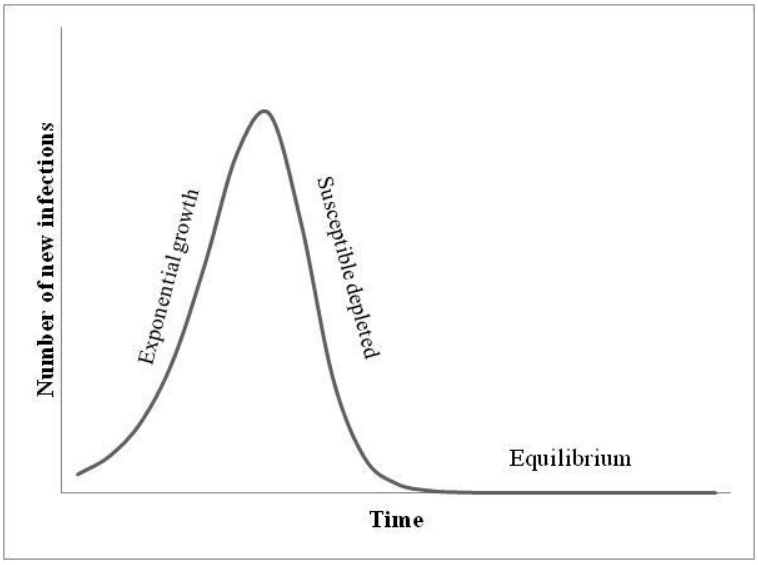

Figure 2. Number of new infections projected by basic SIR model

The basic SIR model assumes all susceptible people are equally at risk of infection from any infected individual and all infected individuals have an equal infectiousness. While this high level aggregation is not able to present the diverse behaviors affecting disease transmission among different subpopulations, a more sophisticated SIR model incorporates mixing patterns of varying degrees based on the population structure. Examples of more sophisticated SIR models include those used in smallpox studies (Ferguson, N. M., et al., 2003). These models capture a variety of mechanisms of transmission and control policies that are used to address different questions. Hethcote surveys numerous disease models and then derives equilibrium conditions mathematically (Hethcote, H. W., 2000). Additional mathematical models are reviewed in (Diekmann, O. and Heesterbeek, J. A. P., 2000) (Vynnycky, E. and White, R. G., 2010) which show that many disease models now include various disease transmission rates and use different levels of data for studying complex scenarios. In this study, we focus on how disease models interact with intervention policies for controlling epidemics. Previous research related to some of these relationships is now reviewed.

Spatial Transmission

Incorporating detailed data on patterns of population settlement and human migration into disease transmission mechanics can make disease models more realistic. In particular, spatial structure is an essential component to consider when diseases are transmitted between multiple communities. Longini studies how global pandemics are influenced by international travelers; he assumes that transmission occurs as passenger flow through connected locations. He presents a mathematical model for analyzing the geographic spread of infectious disease (Longini, I. M., 1988). Grenfell et al. demonstrate recurrent waves of epidemics for measles in England and Wales based on historical data analysis (Grenfell, B. T., et al., 2001). Bjornstad et al. develop a

Time-series Susceptible–Infected–Recovered model to study the recurrent outbreak of infectious diseases in populations (Bjørnstad, O. N., et al., 2002). Each time section is given a dissimilar transmission rate and the parameters are set based on time series analysis of historical data.

Disease Intervention Decisions and Vaccination Strategies

This area focuses on the effectiveness of intervention policies, exploring different consequences of the introduction of intervention/control policies in epidemic models. Crais et al. estimate the effective reproduction ratio of measles by using 2003-2004 data on reported cases in Niamey, Niger (Crais, R. F., et al., 2006). Assuming that the disease transmission rate is stochastic with a given probability distribution, they determine the minimal vaccination coverage that is required to avert future epidemics. Long et al. develop a co-epidemic model for analyzing the interactions between human immunodeficiency virus (HIV) and tuberculosis (TB) (Long, E. F., et al., 2008). Then the disease outcomes are determined under several intervention strategies. Bauch et al develop an age-structured compartmental model to investigate vaccination campaign strategies in low-income countries (Bauch, C. T., et al., 2009). Populations are allocated into one of the mutually exclusive categories based on their epidemiological status and age. Their model assumes vaccinated individuals in different age groups lose their immunity at different rates and they consider the effects that supplemental vaccination programs have on preventing infections.

Other studies have focused on *vaccination strategies* in a disease control and prevention context. The models utilize contact networks to model the interactions between members of the population and use this information to adjust the rate at which infections spread. For example, Takeuchi and Yamamoto study how disease spreads in a contact network (Takeuchi, F. and Yamamoto, K., 2006). They develop a simulation model to access infection outcomes in

populations. Furthermore, they evaluate several vaccination strategies considering the measures of number of new infections and vaccine demand. Miller and Hyman investigate the decision of selecting subgroup populations to vaccinate to mitigate disease outbreak (Miller, J. C. and Hyman J. M., 2007). Assuming that an infected individual infects each of its susceptible neighbors with some probability in a given contact network, they use models to identify effective vaccination strategies for controlling epidemics.

Table 1 summarizes vaccination strategies that have been applied in practice. The diversity of vaccination strategies is presented noting the target population, stage of epidemic and studies that used the vaccination strategy.

Table 1. Summary of vaccination strategies

Vaccination Strategy	Target Population	Stage of Epidemic	Reference
Ring Vaccination	Select all neighbors who are connected to an infected individual	Post-outbreak (Infected individuals are identified)	(Muller, J., et al., 2000)
Targeted Vaccination	Vaccinate all of the population in an affected location or city	Post-outbreak	(Ferguson, N. M., et al., 2003)
Mass Vaccination	Vaccinate the entire population of a country experiencing or threatened by an outbreak	Preventive / Post-outbreak	(Muller, J., et al., 2000)
Acquaintance Vaccination	Select an individual randomly and vaccinate one of its neighbors	Preventive	(Cohen, R., Havlin, S. and ben-Avraham, D., 2003)
Degree Vaccination	Vaccinate individuals by descending degree	Preventive	(Pastor-Satorras, R. and Vespignani, A., 2002)

The goal of vaccination strategies is to mitigate disease impacts. Most studies emphasize ways of identifying vaccination populations that are most likely to be infected by future transmission, while ignoring vaccine availability due to limited supply or having insufficient cold chain capacity to handle vaccines. The challenge for implementing an effective vaccination strategy is to integrate it with realistic vaccine availability. One of the key contributions of this research is that it integrates supply chain performance with disease transmission dynamics.

Recent disease models have considered various factors including influences from the complex behavior of social networks, stochastic transmission, seasonal outbreaks and vaccination strategies. Despite the existence of numerous studies on these topics, less attention has been paid on connecting disease transmission mechanisms with vaccine supply chains. Currently, the interactions between the two are still not clear. This research develops models to help assess the interactions between disease transmission models and vaccine supply chains. The next section describes a vaccine supply chain model and its applications. This is followed by a discussion of how to link supply chain and disease models, and an application of passive cold devices for vaccine supply chain.

3.0 MODELING OF VACCINE DISTRIBUTION NETWORKS FOR LOW AND MIDELE INCOME COUNTRIES

3.1 INTRODUCTION

Effective vaccination programs have long been viewed as one of the best ways to prevent disease transmission. Yet, the prevalence of infectious diseases is still a grave concern in many low and middle income countries, and millions of people remain at risk for diseases that can be prevented through immunization. According to the most recent World Health Organization (WHO) publication on the state of vaccines and immunization (State of the world's vaccines and immunization, 3rd ed. Geneva, 2009), in 2007, there were still millions of children who did not get the complete set of routine immunizations scheduled for their first year of life. A more recent article (Stack, et al., 2011) indicates that increased rates of vaccination in seventy two of the world's poorest countries could save 6.4 million lives and avert 624 million cases of illness over the next decade. While the problem is most acute in low and middle income countries, it is also relevant to a variety of other stakeholders around the world who support vaccine dissemination in low and middle income countries. These include more developed nations, vaccine manufacturers, organizations like the World Bank, the World Health Organization and UNICEF, as well as numerous non-governmental organizations and charitable foundations.

3.1.1 Background

The Expanded Program on Immunization (EPI) was launched by the WHO in 1974 with the goal of vaccinating children throughout the world (Expanded Program on Immunization, 2011). The original suite of vaccines consisted of Bacillus Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP), oral polio, and measles. Over the years, other vaccines such as Hepatitis B (HepB), Haemophilus influenzae meningitis (Hib), mumps, rubella, and yellow fever have been added to the list, and by 2019, twelve or more additional vaccines will be added to the immunization profiles of low and middle income countries to protect against diseases such as typhoid, dengue, malaria and shigella (Kaufmann, R., et al., 2011). In 1999, the Global Alliance for Vaccines and Immunization (GAVI) was created specifically to extend the EPI program to the poorest countries in the world. The members of this public-private global health partnership include United Nations agencies such as the WHO, UNICEF and the World Bank, public health departments in many countries, major charitable foundations and non-governmental organizations, and vaccine manufacturers. The creation of GAVI provided a major impetus to the distribution and delivery of EPI vaccines, and the alliance has been instrumental in expanding vaccine coverage in many parts of the world.

A major challenge facing policy makers and health administrators in low and middle income countries is that their health care resources are often very limited. More importantly, introducing more of the same types of resources into the public health system is not sufficient in and of itself. There is also a need for efficient use of these resources, and one must consider the entire vaccine supply chain, which includes all of the personnel, systems, equipment and activities required to move vaccines from the manufacturer down to their final recipients. In particular, vaccine supply chains in many low and middle income countries are severely strained

and the possibility that they will be unable to distribute new vaccines places many lives at risk (Kaufmann, R., et al., 2011). Stronger, more efficient, and more robust vaccine supply chains can increase vaccination coverage rates and in turn, reduce disease transmission. However, they face the challenge of being able to adapt quickly to a number of situations that might arise. There are many examples of these including

- introduction of new vaccines,
- changes in vaccine presentations and technologies,
- variations in demand because of migrant populations, changes in birth rates, and poor forecasts,
- unexpected reductions in resources such as cold storage capacities or transportation because of unreliable power and/or equipment,
- movement of healthcare personnel, many of whom have limited training to begin with,
- unexpected epidemics that draw routine resources, and
- changes in governmental priorities.

In order to make good decisions regarding supply chain options such as transportation modes, shipment and delivery patterns and timings, storage and reorder policies, etc., one has to consider not just the logistical issues, but also specific vaccine characteristics as they relate to their development, distribution, and delivery. For example a recent study assesses the impact of different ordering policies on vaccine availability at health clinics in low or middle income countries (Rajgopal J., et al., 2011). In general, the decision making process requires a highly interdisciplinary approach, drawing on expertise from (among other fields) medicine, public health, industrial engineering and information sciences.

In this chapter we develop a general mathematical programming model that can be readily adapted as a planning tool in order to systematically analyze many of the common scenarios relevant to a vaccine supply chain. In the following sections we describe a typical EPI vaccine supply chain, followed by a detailed description of our model of the EPI vaccine distribution network. The model has been adapted to model parts or all of the networks in three different countries (Niger, Thailand and Vietnam) having networks of varying degrees of sophistication. We then discuss several examples of how it has been and can be used, to answer different questions of interest to public health administrators and policy makers in low and middle income countries.

3.1.2 The Vaccine Distribution Network for WHO-EPI Vaccines

A generic supply chain usually has an upstream (or procurement) segment that links suppliers with producers, and a downstream (or distribution) segment that links producers with customers. With EPI vaccines it is convenient to view the vaccine manufacturers and other agencies that provide vaccines to a country as the "suppliers," the point of entry of the vaccines into the country's vaccine distribution system as the "producer," and the vaccine recipients as the "customers." With this analogy, our model is only for the downstream segment of the vaccine supply chain, i.e., from where EPI vaccines arrive in the country to where they are finally administered to patients. This allows us to focus on the planning and operational aspects within the country. We assume that decisions such as who will provide the country with the various vaccines, the amounts to be paid for these, and how much vaccine is brought in on an annual basis, have already been made. Typically, these are centralized planning decisions that are made

by some appropriate arm of the country's government and define constraints within which the downstream distribution network must be run.

A typical EPI vaccine distribution network is composed of a series of procurement, storage, and distribution activities. As most vaccines are temperature sensitive, a cold chain system and the associated technology for vaccine delivery and maintenance are essential components. While minimizing operating costs and vaccine wastage are important, usually the primary objective of the vaccine supply chain is to meet or exceed target vaccine coverage rates set by the country.

The general vaccine distribution network for WHO-EPI vaccines is best understood with the specific example that we provide below for the West African nation of Niger. Vaccine purchases are co-financed by GAVI and the central government of Niger and shipped to UNICEF headquarters in Copenhagen, Denmark. UNICEF then ships the vaccines to the central store in Niamey (the capital city of Niger), which constitutes the top node of a four-level arborescent network. Vaccines then move to one of 8 regional stores at the second level of the network. The central store and several of the regional stores have dedicated walk-in cold rooms in addition to other facilities. A regional store serves somewhere between 3 and 8 different districts, each of which has its own storage facility. There are a total of 42 district stores in Niger, each one typically equipped with chest refrigerators and freezers. Finally, the district stores move the vaccines to clinics within the district. Niger has 695 of these, typically equipped with smaller refrigerators and freezers, and all vaccinations are done only at these clinics; currently 642 of these are operational with refrigerator capacity. The network structure and some storage characteristics for Niger are shown in Figure 3.

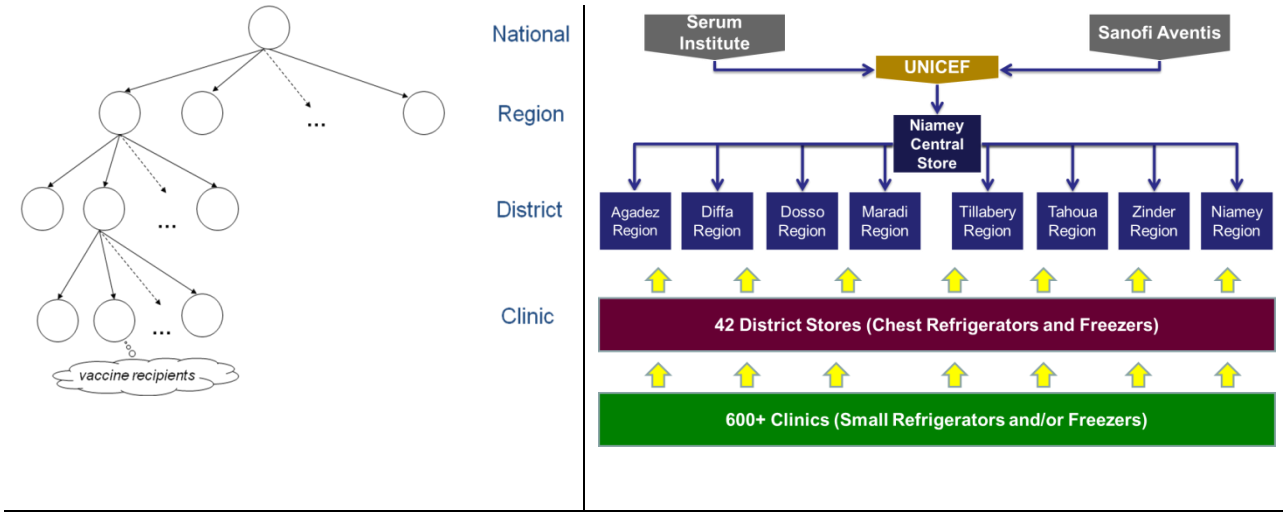

Figure 3. Niger vaccine distribution network

In other countries there might be more or fewer levels in the distribution hierarchy (e.g., Vietnam has provincial stores between the regional and district levels), the nodes at each level might be assigned different names (e.g., clinics are called sub-districts in Thailand), and there might be other minor differences in operational procedures (e.g., in Thailand, vaccinations are also performed at some of the district level nodes). However, the general structure of the network and the operational guidelines are essentially the same: a central/national storage facility where the vaccines arrive and are stored, and from where they flow downwards in a multi-level arborescent network. The timings of the flow could vary. In the simplest case, vaccines might be pushed down to the next lower level at fixed time intervals. In other cases, this might happen at the higher levels, but nodes at the lower levels might pull vaccines from their supplying nodes based on reorder points that are set so as to average approximately the same time interval between pulls. For example, in Niger

- The central store receives shipments from UNICEF in Copenhagen about twice a year.
- Shipments from the central store are pushed down to each regional store once every three months.
- Each district store and clinic has its own reorder point and order quantity; these are set to pull vaccines about once a month on average from its parent node at the next higher level.

3.2. MATHEMATICAL PROGRAMMING MODEL

3.2.1 Overview

We formulate a general mathematical model that can then readily be extended to address several different planning issues relating to the vaccine network. The baseline problem is to determine a distribution strategy to maximize vaccine availability at the lower levels of the hierarchy where the vaccines are administered to patients. Prior research on maximizing the effectiveness of health care resources has been mostly within the context of the developed world and usually for one specific disease at a time as opposed to childhood immunization against several common diseases. For example, Longini et al. (Longini, I. M., et al., 1978), present a deterministic model to select the optimal influenza vaccine distribution pattern among multiple age groups in a "standardized American community" when a limited quantity of vaccine is available. The model specifies heterogeneous mixing patterns among different age individuals and a vaccine distribution can then be determined for each subgroup population to minimize the likelihood of epidemics. Kaplan et al. (2002) use a mathematical model to evaluate various strategies for mitigating the impact of a smallpox bioterrorist attack in a large U.S. city by providing vaccines

to the populations prior to the attack (Kaplan, E. H., et al., 2002). Earnshaw and Hick (2007) use a linear programming model to make decisions concerning the allocation of HIV prevention resources (Earnshaw, S. R. and Hicks, K. A., 2007). The objective is to maximize the number of HIV infection transmissions averted. A related paper is the one by van Wassenhove and Martinez (2010), which addresses humanitarian supply chain issues and the applications of operation research methods in these contexts (van Wassenhove, L. N. and Martinez, A. J. P., 2010). While the focus is not on vaccines, there is some similarity in that vaccines can bear a resemblance to humanitarian relief items (e.g., they are sometimes donated or provided by manufacturers at significantly reduced costs for use in low and middle income countries).

Several extensions to the baseline problem are possible to address with relatively simple modifications of the model. For example, a related problem to consider is capacity allocation/expansion to satisfy changing demand. Many papers have been published using operations research approaches to address these types of issues in other contexts (Melo, M. T., et al., 2009) (Cormier, G. and Gunn, E. A., 1999). However, to our knowledge capacity expansion/allocation in vaccine distribution networks has not been addressed in prior research. This situation is often faced in practice: e.g., the year's budget might allow for a limited set of refrigerators that must then be allocated optimally to nodes in the distribution network.

Another issue of interest to public health officials is the effect on the supply chain of changing the size of a vaccine presentation or of introducing a new vaccine into the suite of vaccines currently being administered. For example, there are plans to introduce the rotavirus and *pneumococcal conjugate vaccine (*PCV) into the list of EPI vaccines in several countries (Pneumococcal vaccination, 2011) (Introduction of Rotavirus vaccines into national immunization programmes: Management manual, including operational information for health

workers, 2009). The rotavirus vaccine comes in several different vial sizes, some of which are relatively large and could possibly have a significant impact on the capability of the cold chains in some countries to handle this and all of the other vaccines in a country's suite of vaccines. Yet another issue of interest is the effect of changes in the structure of the network and/or the distribution policies. For example, what would be the effect of removing an entire level in the hierarchy of the network, or the effect of moving from a monthly to a bi-monthly shipping schedule between two particular levels in the hierarchy?

Table 2. Vaccine characteristics

Vaccine	Doses / Vial	Packed volume c.c. / Dose	Diluent volume c.c. / Dose	Doses Administered	Storage
Scenario: EPI Vaccines (Vaccine volume calculator, 2011) (What are the correct conditions for storing EPI vaccines?, 2011)					
Tuberculosis (BCG)	20	1.2	0.7	1	Refrigerator / Freezer
Tetanus	10	3.0		3	Refrigerator
Measles	10	2.1	0.5	2	Refrigerator
Oral Polio	20	1.0		4	Freezer
Yellow Fever	10	2.5	6.0	1	Refrigerator / Freezer
DTP-HepB-Hib	1	16.8		3	Refrigerator
Scenario : Single-dose measles vial					
Measles-unidose	1	25.6		1	Refrigerator
Scenario: Introducing New Vaccines (WHO prequalified vaccines, 2011)					
Rotavirus	1	17.1		2	Refrigerator
PCV	1	55.9		3	Refrigerator

We address questions such as these by modeling the vaccine distribution network as a linear program (LP). Before describing the details of the model in the next subsection, we first introduce the notion of the "vaccine regimen". Table 2 lists the vaccines that are most commonly

included in the EPI suite of vaccines. With some of these vaccines, only a single dose is required for complete immunization (e.g., BCG, which is typically administered soon after birth), but with others, multiple doses are required at different points in time. As an example, 3 doses of the pentavalent Diphtheria-Tetanus-Pertussis-Hepatitis B-Hemophilus Influenzae type B (DTP-HepB-Hib) are required for complete immunization; these are recommended at 6, 10 and 14 weeks. Similarly, 2 doses of measles vaccine are recommended (the first between 12 and 14 months and the second one at least 4 months later), as are 4 doses of OPV (a primer at birth and 3 subsequent doses). The 3 doses of Tetanus Toxoid are for pregnant women so that they might pass on immunity to their children (Immunization, vaccines and biological, 2012).

The numbers in the "Doses Administered" column of Table 2 constitute what we define as a vaccine "regimen." If we make the simplifying assumption of a stable population with all children and pregnant women adhering to the recommended schedule of immunization, the regimen determines the relative proportions in which we would expect to see demand for doses of the various vaccines at a clinic. Finally, we define a *fully immunized child* (FIC) as one who has received the entire set of vaccines in the regimen and whose mother received the 3 doses of Tetanus Toxoid during her pregnancy.

3.2.2 Model Description

The model is now described in detail. We assume that predefined "units" of each vaccine (e.g., dose) are transported through the supply chain at different monthly time periods over a finite time horizon. Since the focus here is on the vaccine distribution problem, we also assume that vaccine manufacturers can supply enough vaccines to completely satisfy anticipated demand,

which is specified for each location and for each period over the planning horizon. Ideally, we would like to meet all demand or at least some minimum specified fraction of the demand. It is assumed that each location (node) has refrigerator and/or freezer capacity for vaccine storage and that we may or may not have the option of purchasing additional capacity. Depending on their characteristics some vaccines cannot be stored in the freezer while others may be stored in either the freezer or the refrigerator. Some vaccines are shipped in a freeze-dried state and must be reconstituted with diluent prior to being injected. Diluents must also be stored in the refrigerator the day before vaccination day so that the diluent and the vaccines are at the same temperature when the vaccines are reconstituted.

It is assumed that some small known (or estimated) fraction of vaccines is lost in storage and during transportation due to breakage, pilferage, etc., and that some fraction of each vial of vaccine is lost to so-called "open vial waste." The latter term refers to the fact that, for some vaccines when a multi-dose vial is opened during a vaccination session, if the vial is not fully used during the vaccination session then all of the vaccine remaining in the opened vial must be discarded and cannot be used on a subsequent vaccination day (WHO Policy Statement. The use of opened multi-dose vials vaccine in subsequent immunization sessions, 2012). Open vial waste depends on the vial size and the demand during a vaccination session (Lee, B. Y., et al., 2010) and while it is zero in the case of a single dose vial, it could be as high as 80 or 90% for multi-dose vials of vaccines that have low demand. Finally, vaccines may or may not be administered at a node; nodes that only serve as storage or transshipment points are assumed to have zero demand associated with them. Table 3 summarizes the decision variables and parameters for our mathematical models.

Table 3. Decision variables and parameters

Sets of indices	
Index	*Description*
$[I]$	Index set of all vaccines, $i \in [I]$
$[I^R]$	Index subset of vaccines that can only be stored in a refrigerator, $i^R \in [I^R] \subset [I]$
$[J]$	Index set of all nodes in the network, $j \in [J]$
$[T]$	Index set of all time periods in the planning horizon, $t \in [T]$
Parameters	
Parameters	*Description*
$D_{i,j,t}$	Demand (in doses) for vaccine *i* at location *j* in time period *t*
C_j^R	Refrigerator capacity at location *j*
C_j^F	Freezer capacity at location *j*
$C_{k,j}^V$	Transport capacity from location *k* to location *j*
q_i	Effective packed volume of one dose of vaccine *i*
r_i	Diluent volume for vaccine *i*
$\mu_{i,j}$	Average daily demand for vaccine *i* at location *j*
a_i	Number of doses administered of vaccine *i* within the vaccine regimen
$\beta_{i,j}$	Minimum fraction of demand for vaccine *i* at location *j* that must be met each period
u_j^R	Capacity utilization of refrigerators at location *j*
u_j^F	Capacity utilization of freezers at location *j*

Table 3 (continued)

$u^V_{k,j}$	Capacity utilization of transporter from location *k* to location *j*
$w^R_{i,j,t}$	Fraction of vaccine *i* inventory in refrigerators lost at location *j* in period *t*
$w^F_{i,j,t}$	Fraction of vaccine *i* inventory in freezers lost at location *j* in period *t*
$w^{RR}_{i,k,j,t}$	Fraction of vaccine *i* going from a refrigerator at location *k* to a refrigerator at location *j* in time period *t* that is lost
$w^{RF}_{i,k,j,t}$	Fraction of vaccine *i* going from a refrigerator at location *k* to a freezer at location *j* in time period *t* that is lost
$w^{FR}_{i,k,j,t}$	Fraction of vaccine *i* going from a freezer at location *k* to a refrigerator at location *j* in time period *t* that is lost
$w^{FF}_{i,k,j,t}$	Fraction of vaccine *i* going from a freezer at location *k* to a freezer at location *j* in time period *t* that is lost
$w^O_{i,j,t}$	Fraction of open vial loss for vaccine *i* at location *j* in time period *t*
p^R_j	Average procurement cost per unit of refrigerator capacity at location *j*
p^F_j	Average procurement cost per unit of freezer capacity at location *j*
$p^V_{k,j}$	Average procurement cost per unit of transport capacity from location *k* to location *j*

Decision variables

Variable	*Description*
$x^R_{i,j,t}$	Units of vaccine *i* used from a refrigerator to satisfy demand at location *j* in period *t*

Table 3 (continued)

$x_{i,j,t}^{F}$	Units of vaccine *i* used from a freezer to satisfy demand at location *j* in period *t*
n_j	Number of fully immunized children (FIC) at location *j*
$I_{i,j,t}^{R}$	Inventory of vaccine *i* in a refrigerator at location *j* at end of time period *t*
$I_{i,j,t}^{F}$	Inventory of vaccine *i* in a freezer at location *j* at end of time period *t*
$S_{i,k,j,t}^{RR}$	Units of vaccine *i* shipped from a refrigerator at location *k* to a refrigerator at location *j* in time period *t*
$S_{i,k,j,t}^{RF}$	Units of vaccine *i* shipped from a refrigerator at location *k* to a freezer at location *j* in time period *t*
$S_{i,k,j,t}^{FR}$	Units of vaccine *i* shipped from a freezer at location *k* to a refrigerator at location *j* in time period *t*
$S_{i,k,j,t}^{FF}$	Units of vaccine *i* shipped from a freezer at location *k* to a freezer at location *j* in time period *t*
y_j^R	Units of refrigerator capacity added at location *j*
y_j^F	Units of freezer capacity added at location *j*
$y_{k,j}^V$	Units of transport capacity added for the transport link from location *k* to location *j*

Note that while our approach maintains generality, in practice, many of the parameters (e.g., various types of vaccine losses) will probably be identical for different indices of time or location. The baseline model may now be defined as follows:

$$Max \sum_j n_j + \varepsilon \sum_i \sum_j \sum_t \left(x^R_{i,j,t} + x^F_{i,j,t}\right) \qquad \varepsilon \in 0^+ \tag{1}$$

Subject to

$$I^R_{i,j,t} = \left(1 - w^R_{i,j,t-1}\right) I^R_{i,j,t-1} + \sum_{k,k\neq j}\left(1 - w^{FR}_{i,k,j,t-1}\right) S^{FR}_{i,k,j,t-1} + \sum_{k,k\neq j}\left(1 - w^{RR}_{i,k,j,t-1}\right) S^{RR}_{i,k,j,t-1} - \sum_{k,k\neq j} S^{RF}_{i,j,k,t} - \sum_{k,k\neq j} S^{RR}_{i,j,k,t} - x^R_{i,j,t} / \left(1 - w^O_{i,j,t}\right) \qquad i \in [I], j \in [J], t \in [T \backslash \{0\}] \tag{2}$$

$$I^F_{i,j,t} = \left(1 - w^F_{i,j,t-1}\right) I^F_{i,j,t-1} + \sum_{k,k\neq j}\left(1 - w^{RF}_{i,k,j,t-1}\right) S^{RF}_{i,k,j,t-1} + \sum_{k,k\neq j}\left(1 - w^{FF}_{i,k,j,t-1}\right) S^{FF}_{i,k,j,t-1} - \sum_{k,k\neq j} S^{FR}_{i,j,k,t} - \sum_{k,k\neq j} S^{FF}_{i,j,k,t} - x^F_{i,j,t} / \left(1 - w^O_{i,j,t}\right) \qquad i \in [I], j \in [J], t \in [T \backslash \{0\}] \tag{3}$$

$$\sum_{i\in I} q_i \left(\left(1 - w^R_{i,j,t}\right) I^R_{i,j,t} + \sum_{k,k\neq j}\left(1 - w^{FR}_{i,k,j,t}\right) S^{FR}_{i,k,j,t} + \sum_{k,k\neq j}\left(1 - w^{RR}_{i,k,j,t}\right) S^{RR}_{i,k,j,t}\right) \leq u^R_j C^R_j - 1.5 \sum_i r_i \mu_{i,j} \qquad j \in [J], t \in [T] \tag{4}$$

$$\sum_{i\in I} q_i \left(\left(1 - w^F_{i,j,t}\right) I^F_{i,j,t} + \sum_{k,k\neq j}\left(1 - w^{RF}_{i,k,j,t}\right) S^{RF}_{i,k,j,t} + \sum_{k,k\neq j}\left(1 - w^{FF}_{i,k,j,t}\right) S^{FF}_{i,k,j,t}\right) \leq u^F_j C^F_j \quad j \in [J], t \in [T] \tag{5}$$

$$I^R_{i,j,t} = 0 \qquad i \in [I], j \in [J], t = 0 \tag{6}$$

$$I^F_{i,j,t} = 0 \qquad i \in [I], j \in [J], t = 0 \tag{7}$$

$$I^F_{i,j,t} = 0 \qquad i \in [I^R], j \in [J], t = [T] \tag{8}$$

$$\beta_{i,j} D_{i,j,t} \leq x^R_{i,j,t} + x^F_{i,j,t} \leq D_{i,j,t} \qquad i \in [I], j \in [J], t \in [T] \tag{9}$$

$$\sum_{i\in I} q_i \left(S^{RR}_{i,k,j,t} + S^{RF}_{i,k,j,t} + S^{FR}_{i,k,j,t} + S^{FF}_{i,k,j,t}\right) \leq u^V_{k,j} C^V_{k,j} \qquad k\neq j, k, j\in[J], t\in[T] \tag{10}$$

$$n_j \leq \sum_t \left(x^R_{i,j,t} + x^F_{i,j,t}\right) / a_i \qquad i \in [I], j \in [J] \tag{11}$$

All variables ≥ 0

We now describe the various portions of the above model. The primary objective is to maximize the number of fully immunized children (FIC) across all vaccination locations in the network, as captured by the first term in the objective function (1). This is equivalent to maximizing the number of complete regimens that are sent down to the locations where vaccines are administered, subject to demand limits. A secondary objective is to also try and maximize additional doses of vaccines (as partial regimens) that are sent to these locations. The goal here is that even if there is no more space for an entire regimen, we would still like to have other vaccines occupy any space left at the vaccination locations (as opposed to retaining them at transshipment points higher up the chain), thus ensuring that we minimize any unsatisfied demand. This is captured by the second term in the objective and a small value ε is used as a coefficient to ensure that maximizing the number of FIC remains the primary objective.

The first two constraints are inventory balance constraints defined for every vaccine at every location and every time period, in the refrigerator (2) and the freezer (3). The model assumes there is a shipping delay of one time unit, so something that ships to a facility in period t can be used at or shipped out of that facility in period $t+1$. Inventory from the previous period as well as incoming shipments are reduced by appropriate factors to account for storage/transportation losses. If any vaccine is administered at the location, this amount is suitably inflated to account for open vial wastage when computing the inventory actually consumed.

The next two constraints (4) and (5) are storage capacity constraints at the refrigerator and freezer respectively, for each location and each time period. The right hand side specifies effective available capacity by factoring in utilization. Refrigerator capacity is adjusted (4) to reflect the fact that diluents are also stored in refrigerators; the diluent space required is equal to

the diluent volume per dose multiplied by the average daily demand inflated by a factor of 1.5 to account for daily demand variation. Note that the capacity constraint is based on peak inventory. It is assumed that all shipments into a node occur at the beginning of the month, but outbound shipments might not take place immediately, and vaccinations could proceed through the month. Therefore, the peak inventory occurs at the beginning of the period and is equal to the sum of the ending inventory for the previous period plus the inflows at the beginning of the month.

The next three constraints initialize inventories of all vaccines at all locations (6) and (7), and ensure that vaccines that are only stable at refrigerator temperatures (2°C to 8°C) are never stored in freezers (8). Constraint (9) specifies the range of vaccine supply required for each vaccine at each location in each time period. The lower bound in the constraint ensures that in a constrained system every vaccine has at least some minimal amount of supply and that one vaccine type does not dominate the supply at the expense of another.

Vaccine demands ($D_{i,j,t}$) in (9) are calculated based on target populations and vaccine dose presentation. The target population includes children in the age groups indicated by the vaccine administration schedules (e.g., children under age one for tuberculosis) and pregnant women who are expected to be covered under the immunization program. Population data was available only at the district level, and it is assumed that the clinics operating within a district handle equal proportions of the district's population.

Constraint (10) assumes that both freezable and non-freezable vaccines are delivered using a common vehicle type. Thus, the total volume of the vaccine being shipped from one location to another location can never exceed available transporter capacity. Finally, constraint (11) bounds the FIC value over the planning horizon at any location (n_j). The number of

individuals to whom vaccine *i* is administered at location *j* (the right-hand side) is found by dividing the total number of vaccine *i* doses administered at location *j* by the number of doses in the regimen (i.e., the number of doses required by each child to be fully immunized). Then the smallest of these values across all vaccine types constitutes an upper bound on (and hence determines) the value of n_j.

3.2.3 Extension to Allow for Capacity Expansion

Suppose that the baseline system cannot provide sufficient coverage and we would like to add cold storage or transportation capacity in order to achieve full coverage and the goal is to minimize the total capacity investment cost. In that case the objective function (1) is replaced by the new objective below:

$$Min \sum_j \left(p_j^R y_j^R + p_j^F y_j^F\right) + \sum_k \sum_j p_{k,j}^V y_{k,j}^V \tag{12}$$

The decision variables y_j^F and y_j^R represent (respectively) the extra freezer and refrigerator volume needed at location *j*, while $y_{k,j}^V$ represents the extra transportation capacity required along the link from node *k* to node *j*. In addition, constraints (4), (5) and (10) are modified as follows:

$$\sum_{i\in I} q_i\left(\left(1 - w_{i,j,t}^R\right) I_{i,j,t}^R + \sum_{k,k\neq j}\left(1 - w_{i,k,j,t}^{FR}\right) S_{i,k,j,t}^{FR} + \sum_{k,k\neq j}\left(1 - w_{i,k,j,t}^{RR}\right) S_{i,k,j,t}^{RR}\right) \leq$$

$$u_j^R\left(C_j^R + y_j^R\right) - 1.5 \sum_i r_i \mu_{i,j} \qquad j \in [J], t \in [T] \tag{4'}$$

$$\sum_{i\in I} q_i\left(\left(1 - w_{i,j,t}^F\right) I_{i,j,t}^F + \sum_{k,k\neq j}\left(1 - w_{i,k,j,t}^{RF}\right) S_{i,k,j,t}^{RF} + \sum_{k,k\neq j}\left(1 - w_{i,k,j,t}^{FF}\right) S_{i,k,j,t}^{FF}\right) \leq$$

$$u_j^F\left(C_j^F + y_j^F\right) \qquad j \in [J], t \in [T] \tag{5'}$$

$$\sum_{i\in I} q_i\left(S^{RR}_{i,k,j,t} + S^{RF}_{i,k,j,t} + S^{FR}_{i,k,j,t} + S^{FF}_{i,k,j,t}\right) \le u^V_{k,j}\left(C^V_{k,j} + y^V_{k,j}\right) \qquad k\neq j, k, j\in[J], t\in[T] \qquad (10')$$

The right hand sides of equations (4'), (5') and (10') include the addition of non-negative variables y^F_j, y^R_j and $y^V_{k,j}$ respectively, to relieve capacity restrictions by permitting the addition of storage capacity at each of the locations or transportation capacity along each arc as needed to satisfy demand.

3.3 APPLICATIONS

The generic mathematical model of Section 2 can be applied to analyze the vaccine distribution network (or portions of it) for specific countries by using the appropriate data and parameters. In the rest of this chapter, examples of an analysis from the West African country of Niger are reported to illustrate how the model can be used for making vaccine policy decisions.

3.3.1 Data

The structure of the distribution network for Niger was described in Section 1 (see Figure 3). Information on storage and transport capacities was obtained from the EPI program office in Niger. The exact storage capacity at each location is determined based on the equipment that is used for the EPI program. Target populations include pregnant women and children below two years of age. The population estimates are based on the 2005 census and inflated for 2011 using a 3% annual growth rate. Vaccine characteristics are collected from several sources and summarized in Table 2 in Section 2.

3.3.2 Implementation

The mathematical model has been developed using the C++ programming language and solved using the CPLEX 12.2 solver. A total of 17 monthly periods are considered. The output used for analysis is for a one-year period; it excludes the first four time periods and the last time period so as to (i) allow vaccines to flow down to the lowest level in the network and permit sufficient warm-up, and (ii) avoid end of horizon effects. The experiments were run on an Intel Xeon 3.00 Ghz dual-processor PC with 20 GB of RAM. The LP can be solved easily and a solution to the full-scale model can be obtained in a reasonable amout of computing time.

3.3.3 Modeling the Existing System

We start with a model of the system as it exists in order to determine its current capabilies. Our model explicitly takes into account several specific details with respect to cold capacity. The central store at Niamey has a cold room with a gross capacity of 90 m^3. Of the eight regional stores (please refer to Figure 3) the three at Tahoua, Zinder and Maradi currently have cold rooms for vaccine storage (with gross capacities of 40, 30 and 30 m^3 respectively), while another three (at Agadez, Diffa and Dosso) currently have only refrigerators/freezers but no cold rooms. The regional store at Tillabery is completely non-functional, and the district stores in this region are served directly by the central store at Niamey. Also, while the Niamey region exists from an administrative standpoint it does not have it's own cold storage and uses the central store (which is in the same city) to meet demand at its districts. Based on the characteristics of the cold rooms and conversations with personnel, we used a value of 40% for the utilization factor at the cold rooms; so for example, the net capacity at Niamey would be 0.4*90=36 m^3. Finally, for each of

the 53 clinics that does not currently have operational cold storage equipment we assumed its demand was evenly distributed amongst the other operational clinics in the same district.

We focus on two primary performance measures: (i) the country-wide supply ratio (SR_i) across all clinics for each vaccine (i.e., the fraction of total demand for the vaccine that can be met over a one-year evaluation period), and (ii) the average percentage of fully immunized children (*FIC*) across all clinics in the country. If we define φ_j as the total population of patients served by node *j*, these measures are computed via

$$SR_i = \left(\sum_j \sum_t x^R_{i,j,t} + \sum_j \sum_t x^F_{i,j,t}\right) / \sum_j \sum_t D_{i,j,t} \tag{13}$$

$$FIC = 100 \sum_j \left\{\left(\varphi_j / \sum_j \varphi_j\right)\left(n_j / \varphi_j\right)\right\} = 100 \sum_j n_j / \sum_j \varphi_j \tag{14}$$

Note that as indicated by (14), *FIC* might be interepreted as a population-weighted average percentage across all clinics in the country, or as the overall percentage of fully immunized children in the country. Table 4 lists the average *FIC* percentage across clinics in each of the eight administrative regions. While the overall weighted population average for the country is over 87%, it is clear that two of the three regions without cold rooms (Agadez and Dosso) perform poorly; the other one (Diffa) serves a relatively small population and can meet almost all demand with just the refrigerators/freezers at its regional store.

Table 4. Percentage FIC by region

Region	**Percentage FIC at clinics**
Agadez	*41.81*
Diffa	97.19
Dosso	*65.17*
Maradi	85.21
Tillabery	95.12
Tahoua	89.41
Zinder	97.51
Niamey	97.84
Overall	**87.12**

Our observations are confirmed by the fact that Niger's latest Comprehensive Multi Year Plan for 2011-2015 (*cMYP*) recommends the addition of cold rooms of $10m^3$ gross capacity at Agadez and Diffa, and $20m^3$ at Dosso and the currently non-functional Tillabery regional stores (although our results indicate that the cold room at Diffa is probably not necessary).

3.3.4 Modeling Future Scenarios

Next, we illustrate how our model can be used to study several different scenarios that are of interest to policy makers, and discuss our results. The first scenario (titled 'Baseline') is based on adding cold room capacity as recommended in Niger's 2011-2015 *cMYP*, the details of which were listed at the end of Section 3.3. Table 5 and Table 6 contain respectively, (i) the results for

the various vaccine supply ratios, and (ii) the FIC percentages. The second column in each table lists results for the baseline case, while others list results for several other potential future scenarios that will be described in the following subsection. In Table 5, we also present the maximum, minimum and the standard deviation of the *FIC* percentages across all clinics in the country. In addition, Table 7 displays the distribution of the *FIC* percentages across the 642 functional clinics with refrigerator capacity. The reader will be referred to these tables when each scenario is discussed.

Table 5. Vaccine supply ratios for various scenarios

Vaccine	**Baseline**	**Scenario I**	**Scenario II**	**Scenario III Introduction of new vaccines**	
		Regional level removed	**Single-dose measles vial**	**RV**	**RV and PCV**
Tuberculosis	97.58%	97.58%	93.53%	94.33%	83.96%
Tetanus	93.18%	93.19%	77.21%	82.07%	44.97%
Measles	97.58%	97.58%	77.21%	93.49%	83.91%
OralPolio	97.58%	97.58%	93.53%	94.63%	84.58%
YellowFever	97.58%	97.58%	93.53%	93.48%	83.91%
DTC-HepB-HiB	93.18%	93.19%	77.21%	82.07%	44.97%
Rotavirus				82.07%	44.97%
PCV					44.97%

Table 6. Percentage FIC for various scenarios

Percentage of FIC at clinics	Baseline	Scenario I	Scenario II	Scenario III	
		Regional level removed	Single-dose measles vial	Introduction of RV	Introduction of RV and PCV
Weighted Average	93.18	93.19	77.21	82.07	44.97
Standard Deviation	12.2	12.3	23.7	21.1	29.4
Maximum	100	100	100	100	100
Minimum	36.3	34.0	10.5	18.4	0

Table 7. Distribution of percentage FIC across clinics for various scenarios

Scenario	Percentage of clinics with FIC percentages of										
	0% ≤ *FIC* <10 %	**10% ≤ *FIC* <20 %**	**20% ≤ *FIC* <30 %**	**30% ≤ *FIC* <40 %**	**40% ≤ *FIC* <50 %**	**50% ≤ *FIC* <60 %**	**60% ≤ *FIC* <70 %**	**70% ≤ *FIC* <80 %**	**80% ≤ *FIC* <90 %**	**90% ≤ *FIC* <100 %**	***FIC* = 100 %**
Baseline	0.00	0.00	0.00	0.62	1.40	2.50	2.50	1.40	7.63	8.88	75.08
Regional level removed	0.00	0.00	0.00	0.62	1.56	2.18	2.34	1.71	7.63	8.88	75.08
Single-dose measles vial	0.00	0.94	2.18	4.83	6.70	8.26	7.01	6.08	5.14	15.26	43.61
Introduction of RV	0.00	0.16	1.71	4.05	2.18	11.22	3.58	3.43	10.59	9.35	53.74
Introduction of RV and PCV	1.87	14.17	15.58	14.33	11.99	6.08	8.88	4.21	7.48	3.27	12.15

First, the results indicate that the baseline system with added cold rooms is capable of attaining high supply ratios for all vaccines (Table 5) and can also fully immunize over 93% of all children (Table 6). Table 7 indicates that more than three quarters of the clinics can attain an *FIC* percentage of 100%, and the vast majority (91.6%) of them attain an *FIC* percentage of over 80%. The two non-freezable vaccines (Tetanus and DTC-HepB-HiB) determine the limiting value of the *FIC* percentage acheivable; the supply ratios for the other vaccines is larger because of the flexiblity with respect to their storage in either freezers or refrigerators. Furthermore, a few additional doses of the smaller vaccines (OralPolio and Tuberculosis) can be stored even when there is no room for a complete regimen.

Scenario I: *Removal of a Distribution Level from the Supply Network*

Health administrators in Niger were interested in investigating the effects of changing the current four-level distribution supply chain to a three-level one where regional stores are eliminated and vaccines at district stores are obtained directly from the central depot. In this scenario, tranporters at the district level are used to pick up vaccines from the central depot instead of obtaining vaccines from the regional stores. The objective was to see what the effect on final vaccine delivery would be if no new cold rooms were added at regional stores and the existing ones were also eliminated in order to save costs. Because of differences in storage capacities and populations served the answer to this was not obvious.

A model of the new supply chain configuration was analyzed and performance statistics across the 642 operational clinics in Niger are displayed in Table 5, Table 6 and Table 7. Looking at the results it appears that the performance of this system would be almost identical to that of the current four-level hierarchy, with only some very minor differences in the distribution

of the *FIC* percentages across the clinics. This is a key finding since the authorities wanted to ensure that there would be no degradation in performance before considering this option. The next step would be to do a more detailed economic analysis of the savings from eliminating the regional storage facilities, and the increased transportation costs from longer trips between the district and central stores..

Scenario II: *Changing Vial Size*

To improve vaccine safety and efficacy, immunization participants are considering using more single-dose vials to replace commmonly used multi-dose vials. Single-dose vials result in no open-vial waste and they minimize the risk of needle contamination since each vial is only accessed one time (Phillips G., et al., 1989) (Simon, P. A., et al., 1993). Furthermore, they are often integrated with syringes or other injection devices that ensure that vaccines are properly administered (Pre-filled monodose injection devices: a safety standard for new vaccines, or a revolution in the delivery of immunizations?, 2011). An example of an economic analysis of the effects of switching vial sizes can be found in (Lee, B. Y., et al., 2010) while a simulation based approach has also been used in (Lee, B. Y., et al., 2011) (Assi, T. M., et al., 2011) to evaluate the supply chain effects from changes in vial sizes in two different countries.

Applying our model to Niger, we examine the effect of replacing 10-dose measles vials with single-dose vials. As shown in Table 6 the overall average *FIC* percentage decreases by about 16% (from 93.2% in the existing system to 77.2% with single-dose measles vials), while Table 5 indicates that the supply ratios are also reduced for all the vaccines, including the measles vaccine. The reason for this is that even though single dose vials of measles vaccine are more efficient in terms of eliminating open-vial waste and potentially improving vaccine

availability, on a per-dose basis the specific unidose presentation being considered has a significantly larger volume and take up more space, thus crowding out other vaccines. This becomes an issue at clinics with lower capacity. Table 7 also indicates that there is a large decrease in the percentage of clincs that can attain 100% *FIC* percentage and a general increase in the ones which yield a low *FIC* percentage. These results indicate that cold chain capacity can be a factor even when changing the presentation of a single vaccine, and that a system-level view is essential.

Scenario III: *Introduction of New Vaccines*

Many countries are considering introducing new vaccines into their EPI programs. It is important to have a plan to assess the ability of the distribution network to handle these new vaccines in advance of introducing them. As an example, such an analysis would have been invaluable prior to the introduction of two new rotavirus vaccines into several Latin and South American countries in 2006-2007: due to their relatively large volume, the rotavirus vaccines displaced other EPI vaccines from already limited cold storage space in the supply chains. This compromised the distribution of not only the rotavirus vaccines, but also that of other essential routine vaccines, resulting in large numbers of wasted doses and prompting a call for the formulation of smaller presentations of the rotavirus vaccine (de Oliveira, L. H., et al., 2008).

An example of such an analysis using our model can be found in Rotavirus vaccine (RV) and pneumococcal conjugate vaccine (PCV) are being considered for introduction into Niger (Lee, B. Y., et al., 2012). Introducing RV can reduce mortality among children under five years of age in areas that have a high prevalence of diarrheal disease (Introduction of rotavirus vaccines into national immunization programmes: management manual, including operational

information for health workers, 2009). Pneumococcal disease can cause severe complication in young children and outbreaks have occurred in both developing and developed countries, and the intense impact of pneumococcal disease has drawn the attention of public health decision policymakers worldwide (Pneumococcal vaccination, 2011).

The results from the introduction of RV and PCV into the existing network in Niger indicate that the implications are significant. From Table 6, the introduction of RV alone reduces the *FIC* percentage to about 82% (from 93.2% in the current system) with the minimum value falling to 18.4%, while the introduction of both RV and PCV into the regimen reduces the average drastically to under 45%, with three clinics being completely unable to vaccinate *any* of their patients fully (minimum = 0%) because there are insufficient vaccines to distribute at the district level due to storage constraints. Table 7 also shows that with both new vaccines in the regimen there are significant numbers of clinics with very low coverage. With respect to individual vaccines Table 5 shows reductions in the supply ratios for all vaccines, and these reductions are very significant for the larger volume vaccines. Thus, it is obvious that the current distribution network becomes overloaded at many locations when these new vaccines with their large space requirements are introduced into the EPI regimen. The results clearly illustrate that the existing supply and distribution network is not capable of efficiently supporting these new vaccines in their current form. The model also provides details on which specific nodes in the chain are overloaded so that decision makers can prioritize capacity allocation if they decide to go ahead with the new vaccines; this is discussed next.

Scenario IV: *Capacity Expansion*

Vaccines must be kept within a specified temperature range or they can suffer a significant loss of potency (Adu, F. D., et al., 1996) (Lala, M. K. and Lala, K. R., 2003). However, many low and middle income countries have insufficient cold capacity to accomodate vaccine demand (Regional Update: Increasing and sustaining immunization coverage in SEAR, 2011). For many of these countries it would be useful to be able to develop a capacity expansion plan based on information about predicted population sizes and possible changes to the immunization regimens they will use in the future. In the last scenario we examine the capacity implications of the situation studied in the previous subsection, i.e., the introduction of (i) RV and (ii) RV as well as PCV into the EPI vaccine regimen in Niger. Our model lets decison makers analyze their current supply network capacities and explore the impacts on the supply chain of future demand and vaccine scenarios. The model assesses the gaps between the current system and future needs, and extra capacities are determined based on how many vaccines are expected to be handled at each location.

In Niger, vaccines are delivered by different transport devices across the supply network. Cold trucks are used for shipments from the central depot to regional stores. Shipments from regional stores to districts stores are made using 4×4 trucks carrying portable cold boxes. Finally, healthcare workers handle the shipments between district stores and clinics using small vaccine carriers that are usually carried from the district store to the clinic by a worker on a motorcycle, bicycle, or possibly by foot.

Table 8 summarizes the additional capacity needed at each level of the supply chain and for the various transport links. For the baseline case, transportation capacity is clearly not an

issue. Also, there is sufficient capacity at the central store, and relatively minor shortfalls at the regional and clinic levels. However, the district level presents a bottleneck and in order to achieve 100% coverage the network still needs an aggregate cold capacity of a little over 1,000 liters across all of the 42 district stores; our model provides specific additional capacity requirements at each individual store or clinic.

The last two columns in Table 8 list the corresponding values for additional capacity required when (i) RV and (ii) both RV and PCV are introduced into the EPI regimen. It can be seen that there is a capacity shortfall throughout the system. First, if only RV is introduced the central store needs a small increase of about $3m^3$ (to its current net volume of $36m^3$), and the regions also require a small increase. However, at the bottleneck district level the requirements roughly triple over the baseline, and in addition, the clinic level presents a significant problem now with a large increase in the overall capacity required. There is also a need for significantly more cold trucks to transport vaccines between the central store and the districts, although transport capacity at lower levels does not appear to be an issue.

With both RV and PCV in the regimen, the increased requirements over the baseline are drastic and as the last column in Table 8 indicates, the current system is clearly not in any position to handle this satisfactorily. Even at the top of the network, the central store needs to increase its capacity by almost 150%! Transportation capacity requirements also go up very sharply and even at the lowest level (district to clinic) there is insufficient transport capacity. In short, the results clearly indicate that in its current form, the system is marginally equipped to handle the introduction of the Rotavirus vacine and absolutely not equipped to handle both Rotavirus and PCV. Before the latter can be considered, there is a need for significant additional cold storage capacity or for reconfiguring the existing network configuration.

Table 8. Additional net capacity required (liters) for vaccine introduction scenarios

	Baseline	**Introduction of RV**	**Introduction of RV and PCV**
Total Storage Capacity Required			
Central Depot	0	2,842	53,885
Regional Store	34	749	5,147
District Store	1,035	3,038	18,617
Clinics	166	2,285	10,522
Total Transport Capacity Required			
Cold Truck	0	6,892	32,429
4x4 Truck	0	28	4,183
Vaccine Carrier	0	4	4,042

*. Unit: Liters

Table 9. Additional cold storage equipment for vaccine introduction scenarios

Level	**Cold Equipment**	**Baseline**		**Introduction of RV**		**Introduction of RV and PCV**	
		Number	Net Capacity	Number	Net Capacity	Number	Net Capacity
Central	Cold room (36,000 net L each)	0	0L	1	36,000L	2	72,000L
Region	Refrigerator (200 net L each)	1	200L	4	800L	26	5,200L
District	Refrigerator (200 net L each)	17	3,400L	31	6,200L	115	23,000L
Clinic	Solar refrigerator (21 net L each)	54	1,134L	258	5,418L	688	14,448L

To calculate the actual cold equipment required, we use level-specific storage equipment to identify the number of devices needed for each location. The equipment is selected based on the WHO Performance, Quality and Safety (PQS) which recommends cold storage equipment for use in immunization systems in low and middle income countries (PQS devices catalogue, pre-qualified equipment for the expanded programme on immunization, 2011). The strategy of capacity expansion considers vaccine demand, unit cost, unit capacity, maintenance, and physical infrastructure. In general, capacity is expanded by adding a large cold room at the top level, a medium size refrigerator is used at the middle levels and a solar refrigerator is the most recommended solution for the bottom levels due to uncertainty in energy source availability. Table 9 presents a summary of the equipment needed for different vaccine introduction scenarios. For the baseline scenario, there is no need for a cold room, 18 refrigerators are required at the middle levels and 54 solar refrigerators are needed at the clinic level. The net capacities of these devices are reported in the next column. The sum of the net capacity of all of these devices is considerably more than the net capacity shown in Table 9 because many locations only require a few liters but additional capacity must be purchased in discrete units.

3.4 SUMMARY

This chapter provides what is to our knowledge, the first mathematical programming model for a generic WHO-EPI vaccine distribution chain in low and middle income countries. The value of such a model stems from the fact that the general similarity in the overall network structure in different countries makes it easy to adapt it to different environments and public health officials and policy makers in these countries can use the model as a planning and evaluation tool. It can be used to better understand bottlenecks and resource constraints in existing networks so as to

improve vaccine delivery and immunization rates. In addition, it can also be used to evaluate several types of interventions and changes or updates in policy; this was illustrated by the four different scenarios for Niger described in Section 3. Versions of the model have already been used in three different countries. While the work described here is focused on vaccines for routine immunization, in future work we hope to extend and link our model with traditional disease transmission models in order to plan for campaign vaccinations aimed at specific disease outbreaks.

4.0 LINKING THE VMIP MODEL WITH DISEASE MODEL

Many disease transmission models have been analyzed and used for various applications (Hethcote, H. W., 2000) (Anderson, R. M. and May, R. M., 1991) (Diekmann, O. and Heesterbeek, J. A. P., 2000). Recently, models have been modified to capture more details about how diseases spread or to consider population structures more accurately (Ferguson, N. M., et al., 2003) (Vynnycky, E. and White, R. G., 2010). How a disease is transmitted could impact decision making on vaccine distribution, and in this chapter we propose a mechanism that links the vaccine distribution model with a stochastic disease propagation model.

4.1. INTRODUCTION

We investigate the effectiveness of different vaccination strategies and the capital investment required to implement them by using a supply chain model in combination with a disease model. For each strategy, we apply the VMIP to assess vaccine availability. The VMIP also determines optimal capacity allocations if bottlenecks exist in the distribution network. The effectiveness of the different vaccination strategies is evaluated based on the number of new cases of infection that occur. To predict the number of new cases of infection we apply the stochastic disease model of Ferrari et al. (Ferrari, M. J., et al., 2008). It has been widely applied for modeling the spread of measles as part of health care policy development. The model provides an extensive level of detail to segregate outputs and possesses the flexibility to be adapted for various policy

analyses. Figure 4 is a schematic depicting the linkage of the VMIP model with the disease model.

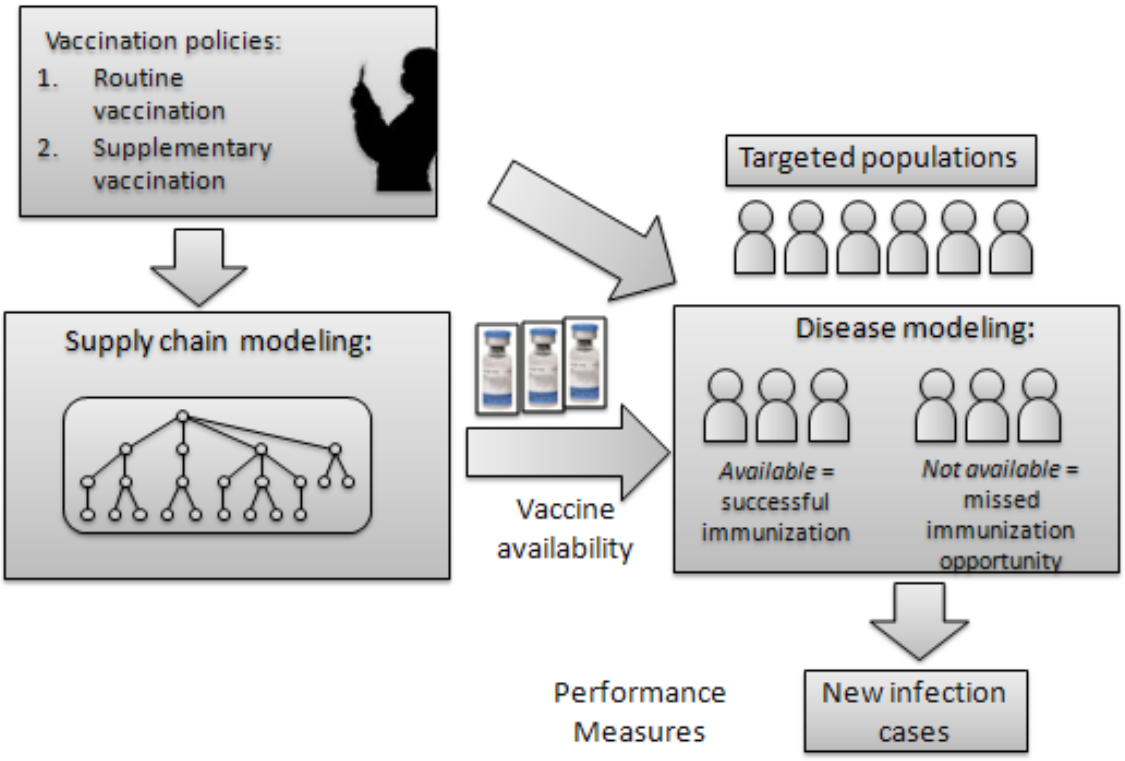

Figure 4. Schematic of linking the VMIP model with disease model

The remaining sections in this chapter introduce the stochastic disease model in detail. The stochastic disease model incorporates randomized factors in order to capture disease dynamics. The model assumes that population age-stratification varies across locations and that birth rates, death rates, contact rates and recovery rates depend on the specific ages found in the populations at different locations. Vaccine distribution decisions usually focus on a specific population class, especially for the age groups that are more likely to be infected (Expanded

Program on Immunization, 2011). The stratifications of population structure provide the capability to answer vaccine distribution questions.

Many infectious diseases tend to have seasonal outbreaks over years. To set an immunization strategy for diseases eradication, it is important to understand long-term epidemic trends and the variations found in seasonal transmission patterns. The epidemic dynamics of measles is the best understood among acute infections and has attracted the attention of many researchers (Bjørnstad, O. N., et al., 2002) (Crais, R. F., et al., 2006) (Grenfell, B. T., et al., 2001). These models study how disease spreads in populations over time and the models' outcomes and conclusions about different control strategies for measles can be useful in providing suggestions for decision making on disease prevention policies.

Most pandemics are related to human migration patterns and increased international travel could lead to global infections (Grenfell, B. T., et al., 2001) (Ruan, S., et al., 2006). With modern transportation networks, worldwide spread of infectious agents becomes much easier. Studies of how diseases spread between locations provide an opportunity to assess the potential for epidemics and to evaluate the effectiveness of different control measures. The goal is to understand the behavior of how diseases spread globally to reduce the risk of pandemics. Using information about population settlements and accumulating cases, several epidemiological studies give quantitative assessments of the epidemic potential of diseases and the effectiveness of control measures (Grenfell, B. T., et al., 2001) (Bosch, F., et al., 1990). We apply a stochastic disease model to investigate spatial transmission effects. The likelihood of transmission is considered as a power function of the distance between susceptible and infected individuals. Disease is more likely to occur in specific geographic areas that are near the primary infection

location. The disease is assumed to be transmitted from place to place by spatially contagious diffusion.

Modeling of countrywide epidemics is a great challenge. This analysis does not consider all factors present in real situations. The key factors included in this analysis are:

- Age-specific force of infection
- Seasonality
- Spatial spread
- Recurrent outbreaks
- Consideration of vaccinations
- Consideration of different levels of vaccine availability

Before applying a disease model for assessing a countrywide immunization policy, real world data is collected and analyzed. In this study, the parameters for the stochastic disease model are estimated based on the census of reported cases and population in Niger over several years. This information is retrieved from several sources (Vynnycky, E. and White, R. G., 2010) (Mossong, J., et al., 1999). Further details are described in the parameter estimation sections.

4.2 STOCHASTIC DISEASE MODEL FORMULATIONS

The development of a disease model is driven by disease biological characteristics. For measles, the disease model classifies individuals into susceptible, infected and recovered compartments. The model considers *m* geographical locations. There are 42 districts in Niger, the model combines the three districts in Niamey into a single location, the Tchirozerine district is merged

with the Agadez district and the Tchintabaraden district is merged with the Abalak district; the result is that 38 locations are considered. The model assumes that all members of a population with the same age that live in the same location are homogenous; that is, they have the same biological and epidemiological parameters.

Let $S_{a,t,m}$, $I_{a,t,m}$, $R_{a,t,m}$ and $P_{a,t,m}$ denote the number of susceptible, infected, recovered and vaccinated people of age *a* who are present in location *m* at time *t*. Due to the nature of measles, the model assumes that individuals who are in the infected class cannot move into the vaccinated class even if they are vaccinated. Population members in the susceptible or recovered compartments may move into the vaccinated class once they have received vaccines. Residents in the susceptible class are assumed to become infected with a certain probability. The average number of people that transition from the susceptible state to the infected state is given by $I^{S}_{a,t,m}$. Each infected individual transitions from the infected state to the recovered state with rate $R^{I}_{a,t,m}$. Further, the model considers that there are unreported cases of infection with a rate of $I^{M}_{a,t,m}$.

The model uses a discrete time step of two weeks that reflects the duration of a typical measles infection (Anderson, R. M. and May, R. M., 1991). In addition, transmission between locations is possible when a measles outbreak occurs in a country. The model assumes that transmission among locations is a power function of the distance between the locations.

Unvaccinated newborns (or non-immune newborns) enter into the susceptible state. Each susceptible individual can either become infected, recovered or vaccinated. An infected individual only becomes recovered. It is also possible that individuals die during infection. For this case, the model assumes that the infected individuals enter the recovered state and then deaths occur in the recovered state. For measles, most individuals will develop permanent

immunity when they recover from an infection or are vaccinated. The compartments and flows are described in the diagram below:

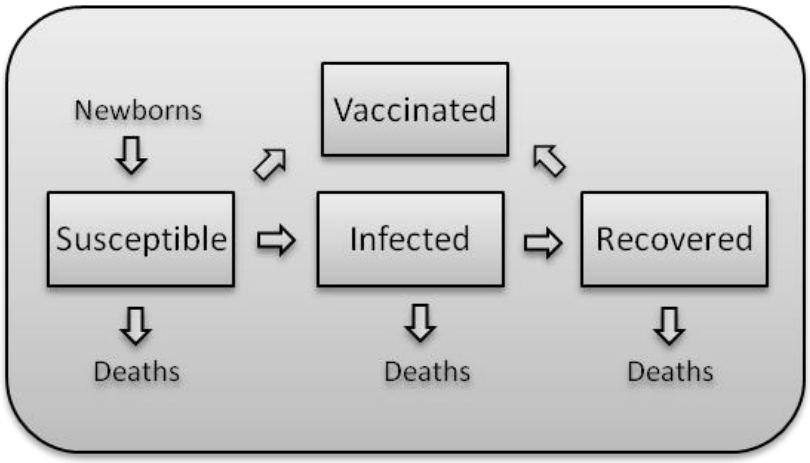

Figure 5. Disease model compartments

4.2.1 Model Formulations

The following table includes the notations that are used in the stochastic disease model.

Table 10. Summary of notations

[Variable Indices]

A the set of age groups, $a = \{0,1,2,3, \dots\}$

T the set of time intervals, $t = \{0,1,2,3, \dots\}$

M the set of locations, $m = \{1,2,3, \dots\}$

[Variables]

Table 10 (continued)

$v_{t,m}$	the expected number of births in period *t* at location *m*
u_a	the expected rate of age transition from age a to age $a+1$ in a time interval
μ_a	the expected mortality rate at age a
$S_{a,t,m}$	the expected number of susceptible individuals of age a in period *t* at location *m*
$I_{a,t,m}$	the number of infected individuals of age a in period *t* at location *m*
$R_{a,t,m}$	the expected number of recovered individuals of age a in period *t* at location *m*
$I^S_{a,t,m}$	the expected number of newly infected individuals of age a in period *t* at location *m*
$R^I_{a,t,m}$	the expected number of newly recovered individuals of age a in period *t* at location *m*
$I^M_{a,t,m}$	the expected number of unreported cases of age a in period *t* at location *m*
$\lambda_{a,m}$	the vaccination visit rate of age group a at location *m*
$x_{t,m}$	the vaccine supply ratio at time *t* at location *m*
$P^S_{a,t-1,m}$	the expected number of vaccinated individuals in the susceptible state in period *t-1* at location *m*
$P^R_{a,t-1,m}$	the expected number of vaccinated individuals in the recovered state in period *t-1* at location *m*
d	the time interval over which infants have maternally derived immunity, after this time infants become fully susceptible

We now present model formulations for the stochastic disease model. Let *T* be the set of time periods, t = 0, 1, 2, 3…, over the given time horizon. Set *M* is the set of locations. For example, there are *M*=38 districts in Niger. For each location, the population is further stratified by different age groups. Set *A* represents the ages of individuals, *a*=0 indicates newborns; numbers greater than 0 indicate age groups of children. The number of annual births varies across the 38 districts in Niger, v_m represents the expected number of births at location *m* during a two week interval.

The age of a population increases when time advances in the simulation runs. The model uses an age transition rate to characterize the population ageing phenomenon. Let u_a be the expected rate of age transition from age a to age $a+1$ in a time interval. Then u_a is equal to the scale of the time interval divided by the unit of the age group. In our case, the scale of the time interval is two weeks and the unit of an age group is four weeks, therefore, the age transition rate is 0.5. Each age group has a different mortality rate, and μ_a is the expected mortality rate at age *a*.

Next, we describe the variables for representing the numbers of individuals in the different compartments. Let $S_{a,t,m}$ denote the expected number of susceptible individuals of age a in period t at location *m.* Similarly, $I_{a,t,m}$ is the number of infected individuals of age a in period t at location *m,* and $R_{a,t,m}$ is the expected number of recovered individuals of age a in period *t* at location *m*.

We also need variables to describe how individuals transition between compartments during each time period. $I^S_{a,t,m}$ is the expected number of newly infected individuals of age *a* in period *t* at location *m*. $R^I_{a,t,m}$ is the number of newly recovered individuals of age *a* in period *t* at

location *m*. It is assumed that the transmission rates vary for different age groups at different time units at different locations. The estimation of transmission parameters will be described in the next section. The number of newly infection individuals is:

$$I^S_{a,t,m} = \beta_{a,t,m}\, S_{a,t,m}\, I_{a,t,m} \tag{1}$$

The model assumes that all infected individuals become recovered at the next time period. Therefore, $R^I_{a,t,m}$ is equal to $I_{a,t,m}$.

Before describing the equations governing each compartment, we present the equations to determine the number of vaccinated individuals in either the susceptible or the recovered state. For simplicity, the model assumes infected individuals will not be vaccinated. Due to a lack of vaccination records and limited resources for conducting blood tests, members of the recovered population may receive vaccines. Campaign vaccinations target specific age group populations regardless of their immunization history. Let $P^S_{a,t-1,m}$ be the susceptible individuals of age *a* who are vaccinated at the previous time period at location *m*. $P^S_{a,t-1,m}$ is equal to the visit rate $\lambda_{a,m}$ multiplied by the vaccine supply ratio $x_{t-1,m}$ and the uninfected susceptible population. The number of uninfected susceptible individuals is defined as $S_{a,t-1,m} - I^S_{a,t,m}$. Therefore, the number of vaccinated individuals in the susceptible state is:

$$P^S_{a,t-1,m} = \lambda_{a,m}\, x_{t-1,m}\, (S_{a,t-1,m} - I^S_{a,t,m}) \tag{2}$$

Let $P^R_{a,t-1,m}$ be the expected number of vaccinated individuals in the recovered state. The number of vaccinated individuals in the recovered state is:

$$P^R_{a,t-1,m} = \lambda_{a,m}\, x_{t-1,m}\, (R_{a,t-1,m} - \mu_a R_{a,t-1,m}) \tag{3}$$

The above equations describe the transition rates between disease states. In the next section, we begin to formulate the equations for determining the size of the populations in each compartment.

- *Susceptible Individuals*

The susceptible individuals include individuals who have not been infected or vaccinated before. One example of a subpopulation in this category is newborn children. For measles, maternally derived immunity in infants covers the first four months (Anderson, R. M. and May, R. M., 1991). The time delay d, accounts for newborn children having a period of immunity before they become susceptible.

Let $S_{a,t,m}$ denote the expected number of susceptible individuals of age a in period t at location m. The equations governing the number of susceptible individuals for different age groups are described as follows.

(I) if the age is 0:

$$S_{a,t,m} = S_{a,t-1,m} + v_{t-d,m} - u_a S_{a,t-1,m} - I^S_{a,t,m} - P^S_{a,t-1,m} - \mu_a S_{a,t-1,m} \quad (4)$$

$$a = 0, \forall t \in \mathrm{T}, \forall m \in \mathrm{M}$$

Here the equations determine the number of susceptible individuals, $S_{a,t,m}$. On the right hand side of the equation, the first term is the number of susceptible individuals from the prior period. The second term is the number of births in period $t - d$. The third term is the population from the previous period that is reaching age 1. The fourth term is the number of newly infected individuals entering the infected compartment. The fifth term

is the vaccinated population. Finally, the sixth terms captures the number of individuals who die.

(II) if the age greater than 0 and less than A:

$$S_{a,t,m} = S_{a,t-1,m} + u_{a-1}\, S_{a-1,t-1,m} - u_a S_{a,t-1,m} - I^S_{a,t,m} - P^S_{a,t-1,m} - \mu_a S_{a,t-1,m}$$

$$0 < a < A, \forall t \in \mathrm{T}\,, \forall m \in \mathrm{M} \tag{5}$$

(III) if the age equals to A:

$$S_{a,t,m} = S_{a,t-1,m} + u_{a-1}\, S_{a-1,t-1,m} - I^S_{a,t,m} - P^S_{a,t-1,m} - \mu_a S_{a,t-1,m} \tag{6}$$

$$a = A, \forall t \in \mathrm{T}\,, \forall m \in \mathrm{M}$$

For the age groups greater than zero, the new number of susceptible individuals is equal to the number susceptible from the prior period plus the inflow from the younger population, minus the population transitioning to the next age, the number newly infected, the number vaccinated and the number of deaths.

- *Infected Individuals*

The expected number of infected individuals of age *a* at the end of period *t* at location *m* is given by:

$$I_{a,t,m} = I_{a,t-1,m} + I^S_{a,t,m} - R^I_{a,t,m} + I^M_{a,t,m} \qquad \forall a \in A\,, \forall t \in \mathrm{T}, \forall m \in M \tag{7}$$

, where $R^I_{a,t,m}$ is the expected number of newly recovered individuals of age *a* at the end of period *t*. The model assumes all infected individuals become recovered at the next time epoch, therefore, $I_{a,t,m}$ equals $I^S_{a,t,m}$ plus $I^M_{a,t,m}$.

- *Recovered Individuals*

The expected number of recovered individuals at time step *t:*

$$R_{a,t,m} = R_{a,t-1,m} + R^{I}_{a,t,m} + u_{a-1}\, R_{a-1,t-1,m} - u_a R_{a,t-1,m} - P^{R}_{a,t-1,m} - \mu_a R_{a,t-1,m}$$

$$\forall a \in A\,, \forall t \in \mathrm{T}, \forall m \in M \tag{8}$$

The number of newly recovered individuals is determined by the number from the prior period and the newly recovered individuals. The third term is the inflow of recovered individuals from the younger population. The fourth term is the outflow of people moving to the next age. The fifth term denotes the vaccinated population. The sixth term denotes deaths that occur in the recovered state.

4.3 PARAMETER ESTIMATIONS

Parameter estimation is a fundamental component of the development of a stochastic disease model. The model uses parameters with different levels of detail as inputs to present disease transmission processes. These parameters are not directly measurable, and must be computed from data in order to calibrate the model to specific problems.

One of the challenges in disease modeling is data collection. Obtaining full observational data can be time consuming and expensive and so it is generally not feasible to collect data at the spatial and temporal frequency required to track these changes effectively. In the absence of complete information on the reported cases, several approaches have been developed to estimate disease parameters. These approaches consider one or more of the nature of the disease, time

series, age structure, population settlements and environmental impacts. The following sections describe common approaches that are applied for estimating disease transmission parameters.

4.3.1 Estimation of Seasonal Transmission

The Time Series SIR (TSIR) model captures the seasonal transmission pattern and the mixing factor between susceptible individuals and infected individuals (Bjørnstad, O. N.et al., 2002). The model parameters are estimated by using observed disease cases and births in an attempt to compensate for the lack of complete data. The subpopulations in each epidemic state can be represented by the equations below:

$$I_t = \beta_t S_{t-1} I_{t-1}^{\alpha} \epsilon_t \tag{9}$$

$$S_t = S_{t-1} + V_{t-d} - I_t + \sigma_t \tag{10}$$

A time step of two weeks is used in the model based on the infection period for measles. In equation (1), β_t is the transmission parameter which varies with the time periods. α is the mixing parameter; if $\alpha > 1$, then the disease will spread more rapidly, otherwise, it will decrease the speed of transmission. Newborns, V_{t-d}, enter the susceptible compartment at time t with delay time d accounting for the length of maternally derived immunity in infants, where d is 16 weeks for measles (Anderson, R. M. and May, R. M., 1991). Both ϵ_t and σ_t are random noise factors with means equal to zero.

There are two stages to fit the system of equations with the observed data. The first stage uses equation (10) to estimate the reporting rate of infected cases, thereby updating the susceptible compartment. Then equation (9) can be fit using the modified number of susceptible

individuals and infected cases based on the results from using equation (10). The detailed description of each stage is as follows:

Stage1. Rebuilding the Susceptible Individuals and Unreported Cases

Suppose C_t is the number of reported cases. Then the number of true cases I_t is

$$I_t = \rho C_t \tag{11}$$

where $\rho = 1$ implies that all cases are reported and values greater than 1 represent the rate at which cases go unreported. Replacing I_t with ρC_t in equation (10) yields

$$S_t = S_{t-1} + V_{t-d} - \rho C_t + u_t \tag{12}$$

Let Z_t denote the deviation of S_t from its mean, so that $S_t = \bar{S} + Z_t$, where $\bar{S}$ is the mean of S_t. Then

$$Z_t = Z_{t-1} + V_{t-d} - \rho C_t + \sigma_t \tag{13}$$

Note that

when $t = 1$, $Z_1 = Z_0 + V_{1-16} - \rho C_1 + \sigma_1$

when $t = 2$, $Z_2 = Z_1 + V_{2-16} - \rho C_2 + \sigma_2$

…

when $t = i$, $Z_i = Z_{i-1} + V_{i-16} - \rho C_i + \sigma_i$

Therefore, (13) may be expressed as

$$Z_t = Z_0 + \sum_{i=1}^{t} V_{i-16} - \rho \sum_{i=1}^{t} C_i + \sum_{i=1}^{t} \sigma_i \tag{14}$$

Furthermore, $\sum_{i=1}^{t} \sigma_i$ is close to zero when *t* is large, so that equation (14) can be rewritten as

$$\sum_{i=1}^{t} V_{i-16} = (Z_t - Z_0) - \rho \sum_{i=1}^{t} C_i \quad (15)$$

Equation (15) is a linear regression model that depicts the relationship between cumulative reported cases and cumulative births. Thus, the set of data pairs $(\sum_{i=1}^{t} C_i, \sum_{i=1}^{t} V_{i-16})$ determines a straight line with slope ρ and intercept $(Z_t - Z_0)$.

Stage 2. Fitting the Transmission Equation

The transmission equation (9) is used to determine new infection cases. Applying a logarithmic transformation to both sides of the equation, we obtain:

$$ln(I_t) = ln(\beta_t) + ln(S_{t-1}) + \alpha\, ln(I_{t-1}) + ln\,(\epsilon_t) \quad (16)$$

Then using a first-order approximation for S_t in terms of its deviation Z_t we have

$$ln(S_t) = ln(\bar{S} + Z_t) \approx ln(\bar{S}) + \frac{Z_t}{\bar{S}} + O(\frac{{Z_t}^2}{\bar{S}^2}) \quad (18)$$

Ignoring the remainder term in (18), and using this to replace S_t in equation (16) yields

$$ln(I_t) = ln(\beta_t) + ln(\bar{S}) + \frac{Z_{t-1}}{\bar{S}} + \alpha\, ln(I_{t-1}) + ln\,(\epsilon_t) \quad (19)$$

Combining the first and second terms in equation (19), we can rewrite it as

$$ln(I_t) = ln(\bar{S}\,\beta_t) + \frac{Z_{t-1}}{\bar{S}} + \alpha\, ln(I_{t-1}) + ln\,(\epsilon_t) \quad (20)$$

By definition $I_t = \hat{\rho} C_t$, where $\hat{\rho}$ is the estimated reported rate and is obtained from the first stage.

$$ln(\hat{\rho}C_t) = ln(\bar{S}\,\beta_t) + \frac{Z_t - 1}{\bar{S}} + \alpha\, ln(\hat{\rho}C_{t-1}) + ln\,(\epsilon_t) \quad (21)$$

As the expected number of susceptible individuals $\bar{S}$ is unknown, β_t cannot be found directly. Instead, define ${\beta_t}^* = \bar{S}\,\beta_t$. Equation (21) becomes

$$\ln(\hat{\rho}C_t) = \ln({\beta_t}^*) + \frac{1}{\bar{S}}Z_{t-1} + \alpha\, ln(\hat{\rho}C_{t-1}) + \ln\,(\epsilon_t) \quad (22)$$

Equation (22) presents a generalized linear model. Given $\hat{\rho}$ and Z_t from stage 1 and the observed cumulative reported case C_t, the unknown parameters ${\beta_t}^*$, $\bar{S}$ and α can then be estimated.■

In summary, the procedure for parameter estimation is: (1) Collect data on birth rate and reported incidence, (2) estimate reporting rate and deviations in the number of susceptible individuals, (3) estimate the transmission rate and mixing, (4) conduct sensitivity analysis to verify the model. Figure 6 shows that the scaled time series transmission rates in Niger have a maximum value of 1.

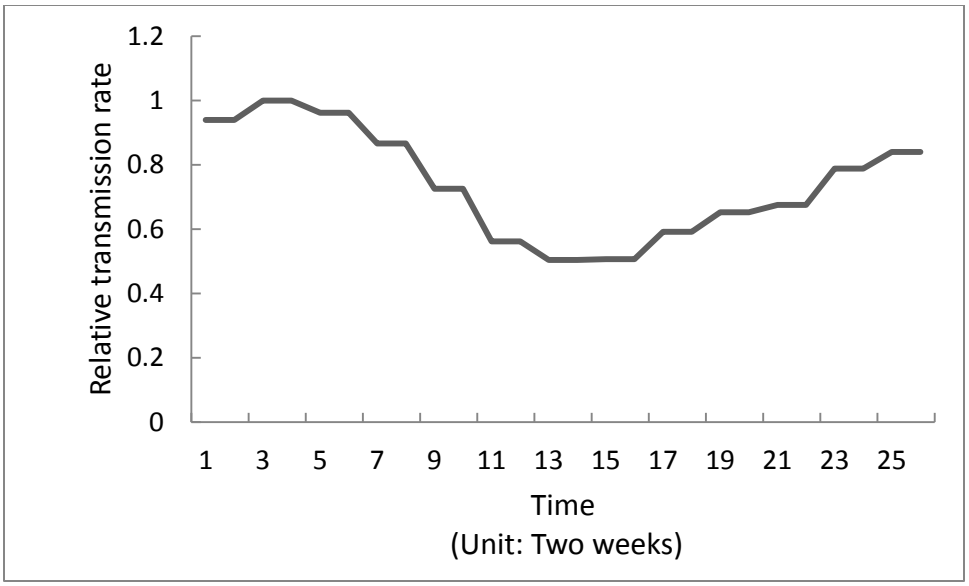

Figure 6. Distribution of estimates of relative time-series transmission rates in Niger

4.3.2 Estimation of Recurrence Outbreak

One of the major challenges with disease models is in capturing the nature of recurrent outbreaks. Extending the TSIR model, the discrete-time compartment model is thus given by

$$I_t = \beta_t S_{t-1}(I_{t-1} + \theta_{t-1})^{\alpha} \tag{23}$$

$$S_t = S_{t-1} + V_{t-d} - I_t \tag{24}$$

where θ represents recurrent infections. Using the assumption that $S_t = \bar{S} + Z_t$ from the previous section, we can rewrite (1) as

$$I_t = \beta_t \, (\bar{S} + Z_{t-1}) \, (I_{t-1} + \theta_{t-1})^{\alpha} \tag{25}$$

Taking logarithms yields

$$ln \, (I_t) = ln \, (\beta_t) + ln(\bar{S} + Z_{t-1}) + \alpha \, ln \, (I_{t-1} + \theta_{t-1}) \tag{26}$$

Replacing $ln(\bar{S} + Z_{t-1})$ with $\ln(\bar{S}) + \frac{Z_{t-1}}{\bar{S}}$ yields

$$ln\,(I_t) = ln\,(\beta_t) + ln(\bar{S}) + \frac{Z_{t-1}}{\bar{S}} + \alpha\, ln\,(I_{t-1} + \theta_{t-1}) \tag{27}$$

I_t and θ_t may temporarily be similar after or prior to extinction ($I_{t'} \approx \theta_{t'}$ when $I_t = 0 \;\; and\; t' = t + or\; t -$), therefore consider a higher-order approximation for $ln\,(I_{t-1} + \theta_{t-1})$

$$ln(I_{t-1} + \theta_{t-1}) = ln(I_{t-1}) + \frac{\theta_{t-1}}{I_{t-1}} - \frac{1}{2}\left(\frac{\theta_{t-1}}{I_{t-1}}\right)^2 + \frac{1}{3}\left(\frac{\theta_{t-1}}{I_{t-1}}\right)^3 + \cdots \tag{28}$$

Let $c_1 = \theta_{t-1}, c_2 = -\theta_{t-1}^2/2, c_3 = \theta_{t-1}^3/3$

$$ln(I_{t-1} + \theta_{t-1}) = ln(I_{t-1}) + c_1 {I_{t-1}}^{-1} + c_2 {I_{t-1}}^{-2} + c_3 {I_{t-1}}^{-3} + \epsilon \tag{29}$$

Thus equation (27) may be restated as

$$ln\,(I_t) = \ln\,(\beta_t) + ln(\bar{S}) + \frac{Z_{t-1}}{\bar{S}} + \alpha\,(ln(I_{t-1}) + c_1 {I_{t-1}}^{-1} + c_2 {I_{t-1}}^{-2} + c_3 {I_{t-1}}^{-3}) + \epsilon \tag{30}$$

Combining the first and second terms and letting $\beta_t^{\,*} = \bar{S}\,\beta_t$

$$ln\,(I_t) = ln(\,\beta_t^{\,*}) + \frac{1}{\bar{S}} Z_{t-1} + \alpha\, ln(I_{t-1}) + \alpha\, c_1 {I_{t-1}}^{-1} + \alpha\, c_2 {I_{t-1}}^{-2} + \alpha\, c_3 {I_{t-1}}^{-3} + \epsilon \tag{31}$$

Equation (31) is a linear regression model with parameter set ($\beta_t^{\,*}, \frac{1}{\bar{S}}, \alpha, \alpha\, c_1, \alpha\, c_2, \alpha\, c_3$) ■

4.3.3 Estimation of Age-Specific Transmission

In this section, we will describe a general age of infection model for estimating transmission rates of different age group populations (Ferrari, M. J., et al., 2010). The model is applied to fit the reported cases from a measles outbreak in Niger. The results for each age-specific transmission rate will be used in the stochastic disease model to conduct a simulation analysis.

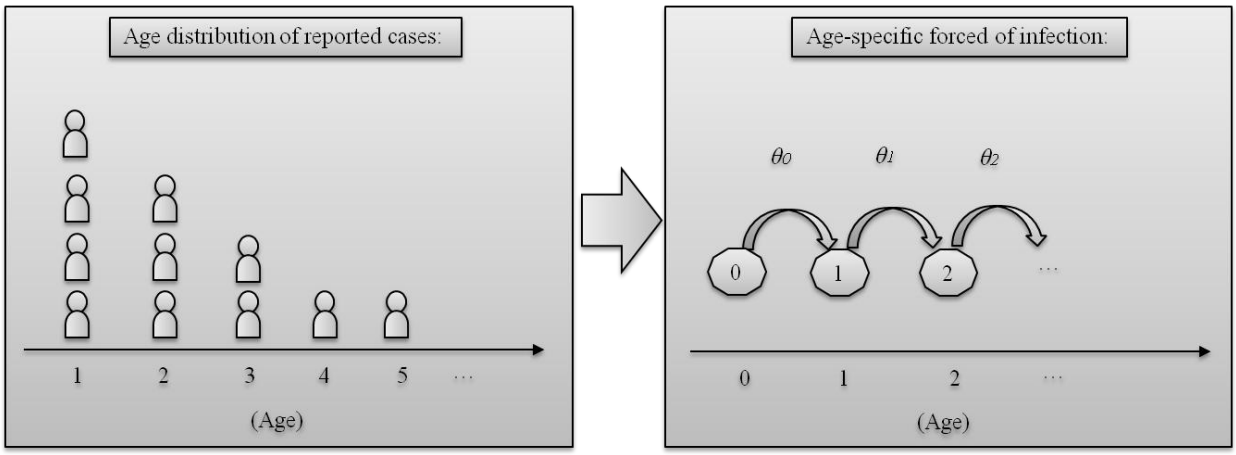

Figure 7. Schematic of estimating age-specific transmission

Let θ_t be the age-specific force of infection. The likelihood of infection at exactly age *i*, denoted by P_i, is the joint probability of not being infected from age 0 to age *i-1* and being infected at age *i*.

$$P_i = \exp\left(-\sum_{t=0}^{i-1}\theta_t\right).(1-\exp(-\theta_t)) \quad (32)$$

In this study, the likelihood of infection at a specific age is based on surveillance data from 2003 through 2004 in Niger. The number of countrywide cases of infection is 11,073. Most cases are of children less than 2 years of age (Ferrari, M. J., et al., 2010). These reported cases are the input data for fitting the parameter θ_t into the equations above.

The next step is to parameterize the transmission rate for each age group based on the results. The estimates of the age-specific force of infection are scaled to the average force of infection across all age groups. Let F_a represent a normalization factor for the infection at a particular age a. Therefore,

$$F_a = \frac{\theta_a}{\sum_{t=0}^{A} \theta_t / A} \qquad \forall a \tag{33}$$

The distribution of the scaled forced of infection is as follows. The peak infection age is 26 months and then the force of infection decreases gradually. Infection risks are low when children are older than 10 years. The first four months are set to zero as maternal immunity allows for full infant immunity to measles (Anderson, R. M. and May, R. M., 1991).

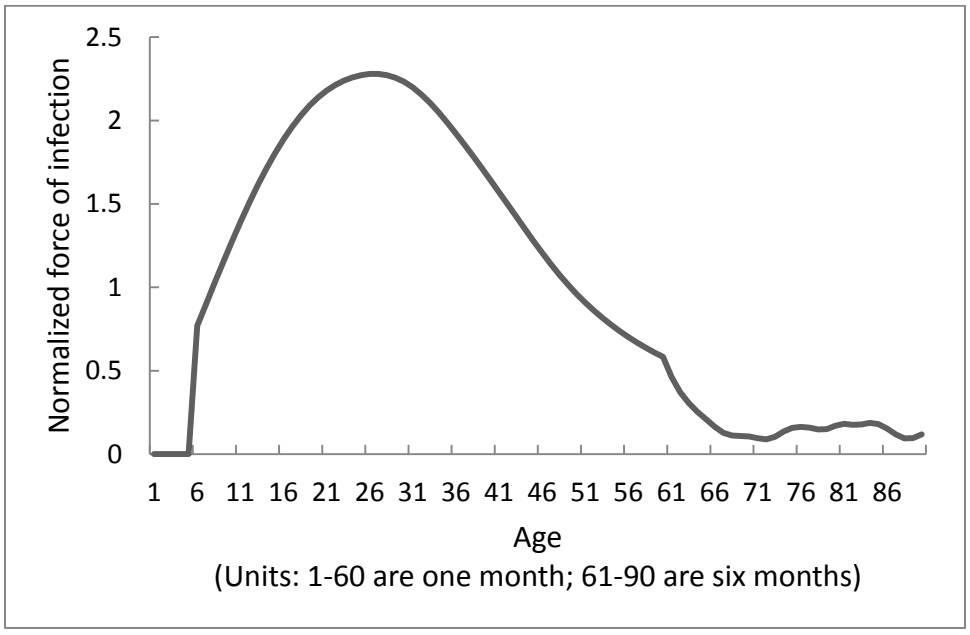

Figure 8. The insensitive of transmission for each age group children

The simulation is based on the age-specific transmission rate, $\beta'_{a,t,m}$, which is adjusted by using normalized force of infection rates.

$$\beta'_{a,t,m} = \beta_{a,t,m} F_a \qquad \forall a, t, m \tag{34}$$

4.4. SIMULATION STUDIES OF MEASLES IN NIGER

Most prior research has focused on disease models. In this work we have introduced a model of the vaccine supply chain. However, healthcare policy makers must consider aspects of both. This section investigates interactions between vaccine supply chains and disease transmission by looking at various measures through an analysis of several different scenarios. To link the disease model with the supply chain model, we use the same geographic distribution of population settlements for both.

4.4.1 Observed and Predicted Patterns of Measles in Niger

No disease model can perfectly predict the nature of a future outbreak. The purpose of these models is to provide evidence-based assessments of the effects of healthcare strategies, and therefore, to help policy makers prepare for epidemics. Instead of performing numerical tests to evaluate the quality of a model, we compare the patterns between actual observed data and the simulated results. Figure 9 shows the plots of month-to-month cases in Niger. The reported cases are collected from countrywide surveillance data during the time period from 1995 to 2004, and then the average monthly cases are presented in Figure 9(b). The Niger reported cases, moves progressively up from January. The number of infections reaches its peak between March and April. After that, the precipitous decline in monthly cases is due to a decrease in the size of the susceptible populations. The average monthly cases in the simulation have a similar pattern when compared to the surveillance data. Figure 9(a) illustrates the simulations results for monthly cases for a time period of fifty years. We exclude the first twenty years of results as warm-up.

The figure indicates that the incidence of disease increases rapidly from January and that the highest number of infections occurs in April.

The high transmission rate of measles primarily leads to acute outbreaks, as shown in both the reported data and the simulation results. Further, there is a strong seasonal effect with many infections in the first quarter. This pattern relates to the heaviest rains that typically occur in March and last until the end of July. The rainy season may heighten risks of more disease outbreaks in Niger (Ferrari, M. J., et al., 2008).

The peak number of infections in the simulated results is higher than the number of reported cases. This is because the simulation considers both reported and unreported cases. In Niger, the measles reporting rate is 56% (Finkenstadt, B. F. and Grenfell, B. T., 2000). After adjusting for the reporting rate, the simulation results match well with the surveillance data.

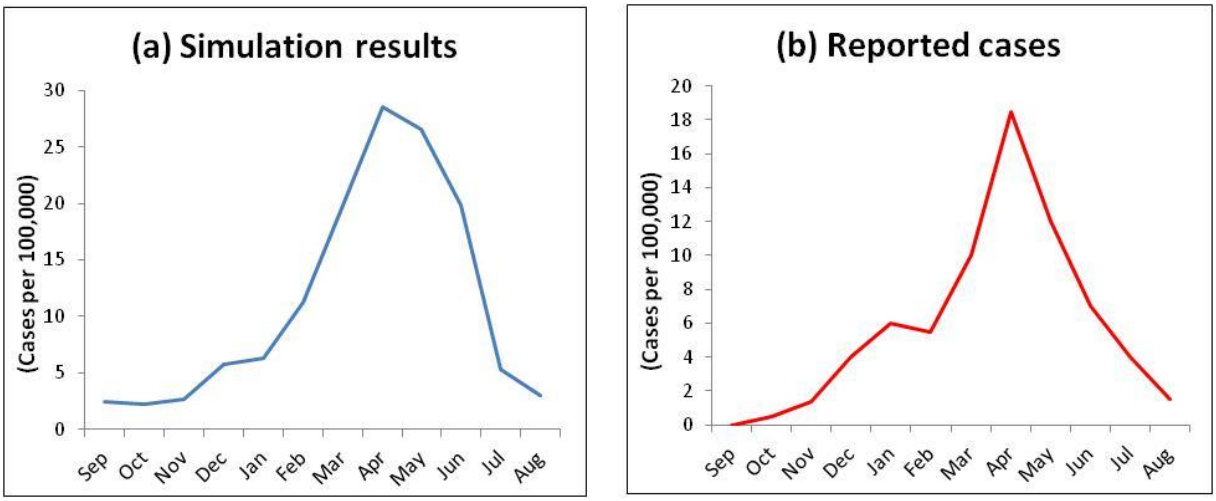

Figure 9. Simulation cases versus reported cases

4.4.2 Niger Studies

We perform sensitivity analysis to make comparisons among different scenarios using the VMIP model and the stochastic disease model. These scenarios include various vaccination strategies and recipient visit rates to assess the relative effects of recommended policies enabling future planning for diseases control.

Vaccination Policy Impact

For Niger, the routine measles vaccine was introduced by EPI in 1987. Routine vaccination demands are based on a vaccination schedule for children of different age groups (for example, the first dose between 6-9 months). Catch-up measles, or supplemental immunization activity (SIA), began in 2004 targeting all children aged 9 months to 14 years old (Hoekstra, E. J., et al., 2011), regardless of their prior history of vaccinations or infections. Periodic follow-up activities vaccinate all populations born since the previous SIA event. The intensive demand ensuing from an SIA is a challenge for vaccine logisticians and can be costly to implement and difficult to conduct in a short time window. To implement an SIA program, several factors are considered, such as vaccine supply, cold chain capacities, required nurses/health workers and accessory devices, all of which are needed for vaccinations. We explore an SIA vaccination campaign of one month duration occurring once every four years during the month of January, and evaluate the operational feasibility in vaccine distribution. Vaccine demands are split evenly over the SIA vaccination campaign duration. To assess vaccine availability, we extend the VMIP model to include both RI and SIA vaccinations. We assume that delivery of SIA vaccines has a higher priority than RI vaccines if the current supply chain has a bottleneck. Table 11 shows that the vaccine availability for measles RI declines slightly when SIA are introduced. The reason for this

is that the SIA vaccinations create a greater load for the cold chain during the time period(s) of the SIA vaccination sessions. For the one month scenario considered here, RI vaccine availability drops by about 0.6% during the SIA.

The impact of vaccination policies on the number of new cases is estimated by applying the stochastic disease model. We report the average number of monthly new cases of measles per 100,000 people (referred to as cases per 100,000 in the remaining discussion). The model predicts that there are 23.6 cases per 100,000 when there is 96.9% vaccine availability for RIs. In the case where supply chain capacities must be shared for RI and SIA, SIA introduction decreases the average monthly number of cases to 20.5 due to the additional SIA vaccinations, although there is a reduction in RI vaccine availabilities as compared with the non-SIA scenario because of insufficient overall capacity. As a result, the total susceptible population sizes for the SIA cases are actually less than the base (RI) case and this leads to fewer infected individuals.

The next case considered is where the vaccines for SIA are stored separately from the standard EPI cold chain, i.e., using separate equipment for these vaccines. This may occur if an outside entity, such as an NGO, organizes a campaign and provides its own cold storage equipment that will be in place temporarily to support the SIA campaign. In this case, the SIA vaccines will not displace the routine EPI vaccines. For purposes of this analysis, we assume the most optimistic SIA scenario where the RI vaccine availability is unchanged and there is 100% SIA vaccine availability. Table 11 shows the disease incidence data – there are 19.6 cases per 100,000 for the SIA as compared with 20.5 cases per 100,000 when the SIA vaccines share supply chain capacity with RI. This indicates the benefit of separating SIA vaccines from the standard EPI supply chain or of providing additional temporary storage capacity to account for the SIA.

Table 11. Vaccination policies performance

Scenario	RI vaccine availability	SIA vaccine availability	Disease incidence*
RI **	96.9%	-	23.6
Supply chain capacities shared for RI and SIA			
SIA***	96. 3%	100%	20.5
SIA does not share supply chain capacities with RI			
SIA***	96.9%	100%	19.6

* Average monthly cases per 100,000
** RI visit rate 78%
*** SIA vaccination was assumed to occur over one month; the SIA visit rate is 7% of the target population

Supply Chain Reinforced

In order to overcome the potential drawback of reduced RI levels associated with SIAs as described in the previous section we next investigate the cold chain capacity requirements for different vaccine polices. The storage capacities will be added in order to remove the current system bottlenecks. The WHO and UNICEF have specific guidelines for adding new equipment for immunization, and all new equipment must be prequalified before being deployed. An example of available equipment for each level is shown in Table 12. Cold rooms are installed at the higher levels for stocking larger amounts of vaccine doses. The lowest level uses solar refrigerators due to the frequent lack of dependable electricity or other energy sources at these locations.

Table 12. Cold chain equipment for immunization

Level	Type	Vaccine storage space	Source
Central and Region	Cold room	30 m^3	Niger comprehensive multi-year plan (cMYP)
District	Ice lined refrigerator (ILR)	105 L	(Prequalified ice-lined refrigerator, 2012)
Clinic	Solar refrigerator	21 L	(Prequalified solar refrigerator, 2012)

The additional cold storage requirements are shown in Table 13. For the RI scenario, the extra storage capacity is 24 ILRs and 58 solar refrigerators across all district and clinic locations in Niger. The storage capacity requirement increases when SIAs are included. The SIA scenario requires the most storage capacity: 24 ILRs at the district level and 106 solar refrigerators at the clinic level.

We assess the performance of the vaccination policies by considering the number of new cases of measles. The scenarios are based on the reinforced vaccine supply chain systems and all the vaccines necessary to satisfy demand can be delivered. The incidence rate for the RI now drops to 16.6 cases per 100,000. The additional capacity fills the vaccine availability gap, and therefore, more children develop immunity by vaccination. Compared with the current system (Table 11), the reinforced supply chain thus reduces the number of expected infections.

With SIA, the incidence rate is now 14.1 cases per 100,000, which is lower than the base (RI) case. This vaccination policy has the best performance in terms of disease incidence as compared with other policies. However, the capacity investment is relatively expensive.

Table 13. Extra capacities required for vaccination policies

		RI **	SIA***
Disease incidence*		16.6	14.1
Cold equipment	Cold room	0	0
	ILR	24	24
	Solar refrigerator	58	106

* Average monthly cases per 100,000
** RI visit rate 78%
*** SIA vaccination was assumed to occur over one month; the SIA visit rate is 7% of the target population

Sensitivity Analysis on Visit Rate

Decision making regarding vaccination strategies for epidemic control is made more difficult due to the high degree of uncertainty associated with patient visit rates. We conduct sensitivity analysis by examining various visit rates in order to explore the impacts on the vaccine supply chain and disease transmission outcomes. The age specific vaccination rates are based on data collected from the Niamey Lot Quality Assurance Sampling (LQAS) during 2003 to 2004. In Figure 10, the solid line represents the actual cumulative visit rate data for routine immunizations. Most children received vaccines before the age of one year and the cumulative visit rate is relative low - about 78%. We examine the impact if the RI visit rate can increase from 78%. For each age group, the visit rate is inflated with a constant ratio to reach the higher cumulative visit rate. For example, the visit rate at each age group is inflated by a multiplicative factor of 1.8 to reach the 95% cumulative visit rate and inflated by a multiplicative factor of 3 to reach approximately 100% (dashed lines in Figure 10).

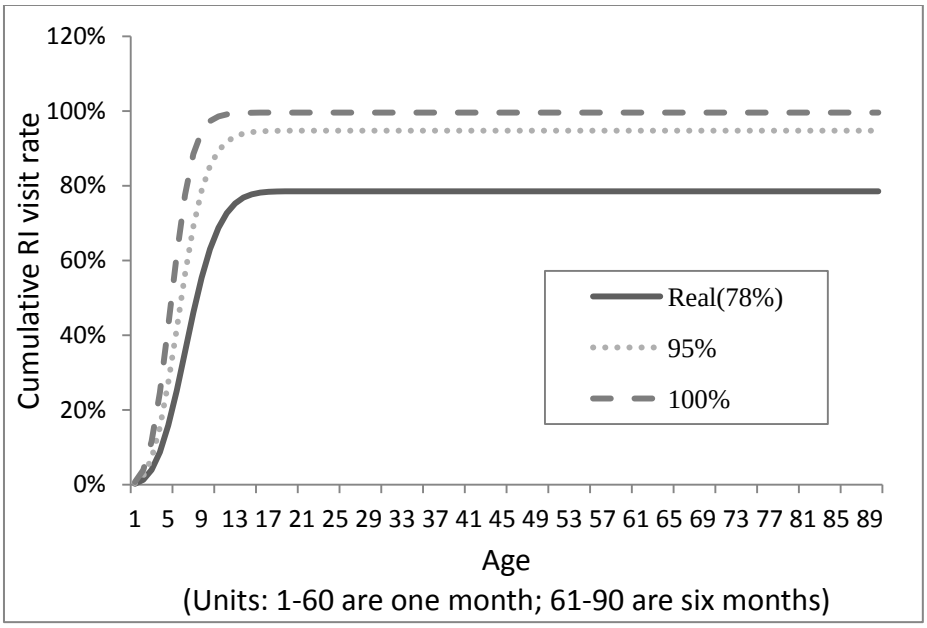

Figure 10. Vaccine recipients visit rate settings for simulation studies

Figure 11 shows the simulation results for the number of new incidences of measles based on different visit rate settings, ranging from the current situation of 78% up to 100%. The results show that new cases decline dramatically with an increase in the visit rate. If the visit rate increases from 78% to 79% the number of new cases drops to about 12 per 100,000 and if the visit rated increases to 82% then the number of new cases drops to about 2.47 per 100,000. If the visit rate is 84% or greater there is virtually no presence of measles in the entire population.

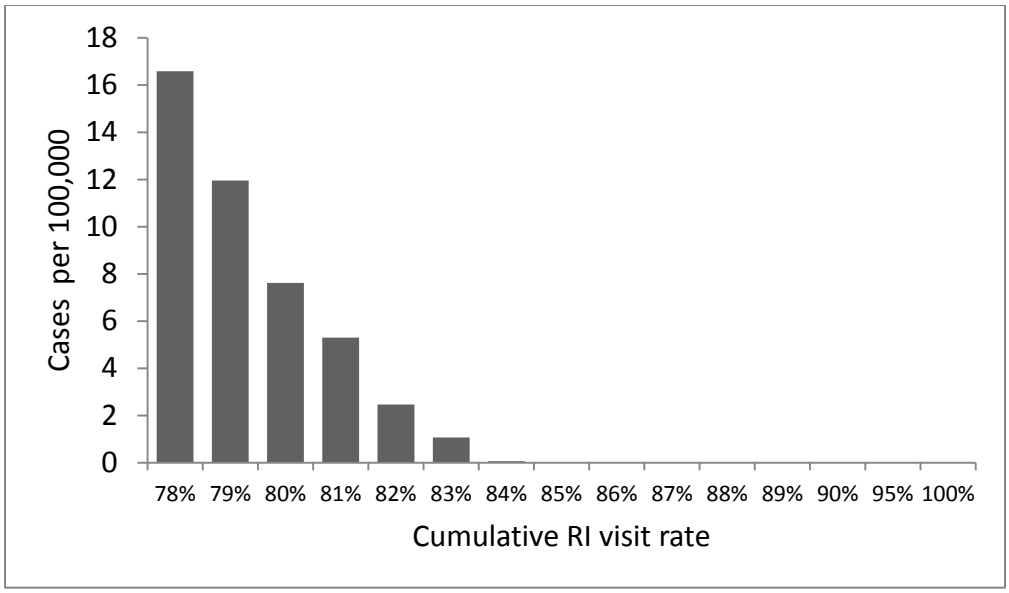

Figure 11. Average incidence rate per month for different RI visit rates

We also conducted a similar analysis changing only the SIA visit rate. For this analysis, we assumed that the SIA vaccinations are completed within one month and the RI visit rates remain the same (78%) and that the vaccine availability is 100%. There are about 14 per 100,000 for the lowest SIA visit rate setting (of zero), 9.8 per 100,000 for the 15% SIA visit rate, and very few incidences for scenarios when the visit rates are great than 60% (Figure 12).

A decision maker could assess the trade-offs of using two different strategies to improve coverage. The first strategy is to increase the visit rates for RI and to eliminate virtually all measles incidences the overall visit rate needs to increase from 78% to 85%. The second strategy would be to increase SIA activities from covering 7% of the target population to covering about 60% of the target population.

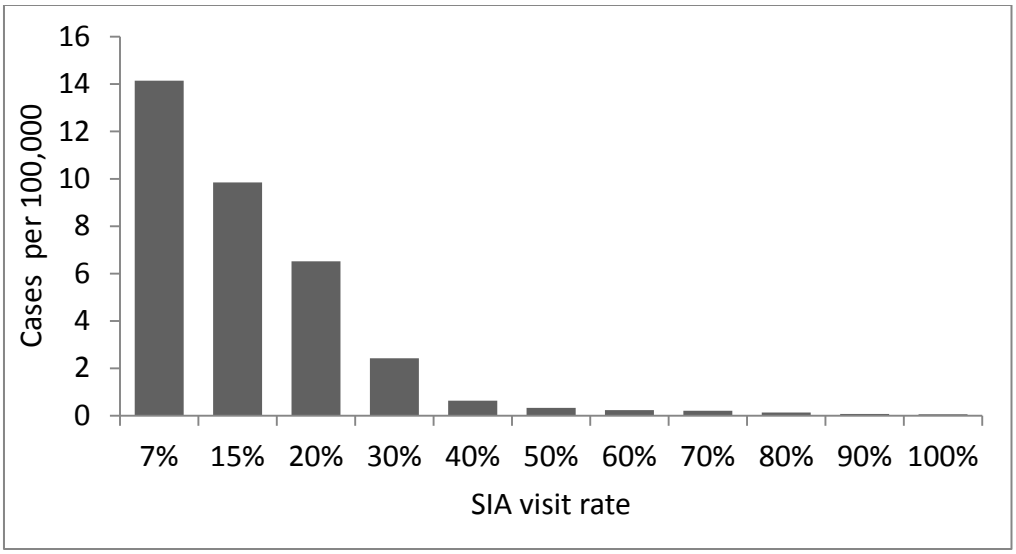

Figure 12. Average incidence rate per month for different SIA visit rates

Next we assess the impact of visit rates on the supply chain. Table 14 shows the additional required cold storage capacities to provide 100% availability for several different visit rate scenarios and the resulting number of new incidences of disease for each scenario. The disease incidence rate is 16.59 per 100,000 in the 78% visit rate case, 7.62 per 100,000 in the 80% visit rate case and the number of new infections approaches zero when the visit rates are greater than 85%. The required storage capacity is 24 ILRs and 58 solar refrigerators for the 78% visit rate. More storage capacity is required when the visit rates are increased, for example, 25 ILRS and 73 solar refrigerators are needed in the 85% visit rate scenario. The 100% visit rate scenario needs the most storage capacity. While improved visit rates can reduce the risk of infections, the greater vaccine demands will require more capacities. However, our findings indicate that the largest reduction of disease incidence occurs when the visit rates rise to 85% from the 78% level which only requires one additional ILR and 15 solar refrigerators to scale up

capacity to fulfill the additional demands. This represents a relatively minor addition for the entire supply chain network.

Table 14. Sensitivity analysis on vaccine recipient visit rates

	Visit rate					
	78%	**80%**	**85%**	**90%**	**95%**	**100%**
Disease incidences*	16.59	7.62	0.03	0.00	0.00	0.00
Number of additional storage equipment						
Cold room	0	0	0	0	0	0
ILR	24	24	25	27	30	33
Solar refrigerator	58	60	73	95	98	105

4.5 CONCLUSIONS

Our study of resource allocation for disease control differs from existing models in that we explicitly model interactions among the vaccine supply chain and vaccination strategies and we apply a stochastic disease model to assess effectiveness in terms of epidemic outcomes. Based on realistic data, both models provide practical strategies to address the interactions between the vaccine supply chain and disease transmission.

We developed procedures that can link a supply chain model with a stochastic disease model for vaccine decision making in Niger. This procedure can be adapted to other countries or different diseases studies. The measures of resources required and benefits associated with changes in vaccination strategies provide valuable information for policy makers to determine the optimal prevention program.

Our analysis has several limitations. The simulation assumes that the vaccines are delivered at the start of the time period and that vaccination effects are instantaneous. It is unlikely that vaccinations could be implemented and be effective instantaneously. Another factor to consider is that in real life recovered individuals may return to the susceptible compartment. The temporal immunization can change immunization decisions. Future work is needed to determine how these dynamic effects may affect the vaccine policy. In addition, we assumed that the vaccine demands are stationary and do not consider human migration. Niger has a high migration rate due to the living style, agricultural economy and climate. However, the existing data on human migration is very limited. More work is needed to characterize these social behaviors.

We found that raising either the RI or SIA visit rates can significant reduce disease incidences. However, in addition to preparing the supply chain to deliver additional vaccines to the vaccinations points, there is the significant challenge of how to actually increase the visit rates. In order to increase visit rates decision makers must allocate their efforts and resources to make vaccinations easier to access, especially in areas with limited health care resources. Such strategies include outreach vaccination, community-based vaccination and campaign vaccinations. In the next chapter, we discuss the application of passive cold devices designed for vaccine delivery at remote vaccination locations.

5.0 PASSIVE COLD DEVICES FOR VACCINE SUPPLY CHAINS

5.1 INTRODUCTION

Passive cold devices (PCD) constitute a novel approach for improving immunization rates in low and middle income countries. PCDs do not rely on energy sources and are therefore highly desirable. They are also easy to rapidly install at any location. PCDs are kept cool using a cooling medium which is a phase changing material. The most common phase changing material is ice and for this reason we simply refer to the phase changing material as ice for the remainder of this discussion. The cooling medium and vaccines are filled in PCDs at a recharging point, and health workers then move the refilled PCD along with vaccination devices (i.e., syringes, etc.) to vaccination points. There are different PCD designs that give rise to different features. This research considers three features: vaccine storage volume, required cooling medium volume, and maximum storage duration. Lighter and more portable PCDs are required for outreach or community-based vaccinations. There are existing storage devices that can be used for short-term storage (e.g., a Dometic RCW4) while other models have a longer storage duration of more than one week at 32°C (e.g., a Dometic RCW25). Presently there is interest in developing PCDs that can store vaccines for weeks or possible months between recharging.

PCDs could be incorporated into the supply chain to replace stationary cold chain equipment at health posts. There are many health posts operating in remote areas with unreliable power sources, limited power availability or high energy costs. For these facilities, PCDs could be used to ensure the storage and transportation needs of vaccines at controlled temperatures.

The benefits of using passive cold devices for storage and transportation may be summarized as follows:

- Easy to access outreach areas
- Not affected by power outages
- Lower probability of equipment breakdown
- Lower recurrent costs (i.e., energy cost and maintenance cost)
- No need for vaccine carriers or cold trucks during transportation

A second related issue is the introduction of new vaccines, which often requires major modifications to existing cold chain systems. While significant progress has been made through global organizations to strengthen cold chain capacities, the delivery and storage of vaccines is costly and requires considerable support including potential equipment maintenance. The recurrent costs of adding cold capacity is a significant concern and in order to provide a sustainable cold chain PCDs could prove favorable when compared with conventional refrigerators.

Cold Chain Equipment

Before implementing an immunization program in a country, decision makers need to evaluate whether the existing cold chain is capable of supporting vaccination activities or not. Many factors must be considered including forecasted vaccine demand, storage capacities, ordering policies, transportation capacities, facility locations, etc. The Effective Vaccine Management (EVM) initiative provides a comprehensive assessment of cold chain system performance (Effective vaccine management initiative, 2012). This identifies capacity expansion strategies for

fixing current problems in vaccine supply chains, as well as it considers future cold capacity needs over a planning horizon of several years.

We now review both conventional cold storage devices and new technologies. To organize the discussion, we classify different types of cold chain equipment and present various plausible use cases for each type of equipment. It should be noted that there are more different types of existing equipment than those discussed here, we only select representative examples from the WHO's list of Performance, Quality and Safety (PQS) prequalified devices and equipment (PQS devices catalogue, pre-qualified equipment for the expanded programme on immunization, 2011).

(1) Active Cold Devices

Cold rooms, refrigerators and freezers are examples of active cold devices. These devices rely on power sources and are installed within facilities. A cold room can hold a very high volume of vaccines, with sizes ranging from 10 cubic meters to 50 cubic meters in order to take advantage of economies of scale. In general, most cold rooms are placed at the central and regional levels and provide service to lower levels. The design of a cold room must ensure good circulation of cold air through the shelves and maintain a stable temperature range. To prevent loss from equipment breakdowns, design recommendations encourage redundant electricity sources and components.

Conventional refrigerators and freezers operate by using electricity, kerosene or propane. Some models use dual energy sources (fuel and electricity) within the same equipment, and have standby units with automatic start up when the main energy source fails. For example, the Sibir 170KE model runs on kerosene or electricity. An ice lined refrigerator (ILR) is another example

of a device that provides stable temperatures when power cuts are a chronic problem. The backup system can provide a temperature range of $2^{o}C$ to $8^{o}C$ for 24 hours during power shortfalls or outages.

A solar refrigerator can be operated in areas that are off the electricity grid. Its self-generator unit can provide electricity for the needs of the refrigerator, as well as power that can be shared for other purposes. In general, the complete system includes solar panels, batteries, and refrigerators. To save on system costs, battery-free solar refrigerators eliminate the need for batteries and charge controllers. These refrigerators are highly efficient with low energy consumption and keep vaccines cold during cloudy weather. A solar refrigerator system needs be installed by a qualified installation company to ensure proper functioning of all components. To ensure that all equipment perform normally, a strong routine maintenance program is also a necessity. This involves regular cleaning of the solar panels, checking cables and connections, and replacing parts and/or batteries periodically. The costs associated with system initialization and maintenance are concerns when considering solar capacity investment.

(2) Passive Cold Devices

The availability of reliable energy at a facility can limit the installation of active cold chain equipment. Many health posts in low and middle income countries have unreliable electricity, frequent power interruptions or high electricity costs. Those factors impact decisions about how to allocate cold chain equipment in remote locations. PCDs typically consist of an insulated container filled with ice packs to keep vaccines cold without using power. There are a variety of passive cold devices available, ranging from cold boxes and vaccine carriers to insulated containers. A vaccine carrier has a relatively small vaccine storage volume and is usually

designed for transporting vaccines to health posts. A typical vaccine carrier might hold three liters of vaccines and maintain proper temperatures for up to about twenty-four hours (Large vaccine carrier: Model RCW4, 2012). A cold box refers to a relatively large insulated container. In practice, a cold box is used for either longer distance transportation or to support outreach vaccinations. In order to have a longer cold life, a larger number of ice packs are filled in the cold box. The cold life can be up to several weeks depending on usage and the frequency with which the cold box is opened and closed.

5.2 USE CASES

We next explore possible applications of PCDs. We use Niger as a pilot for studying PCD applications and our analysis allows generalizability to other countries and to other use cases. Niger is a typical low and middle income country with a high birth rate, low vaccine coverage, poor healthcare facilities, and infectious diseases are still prevalent.

This study investigates using PCDs for delivering vaccines from the district level to the health post level. Vaccine distribution from the central store, through regions and to the districts is the same as before. We assume that the vaccine supply chain would contain enough capacity to accommodate all use cases in this study and would fulfill vaccine demands and ice requirements in a timely manner. At the recharging points (i.e., district stores), PCDs are filled with cooling media (say, ice-packs) and vaccines, and the PCDs are delivered from the district to the health posts by using either a 4×4 truck or motorbike. The selection of the vehicle type depends on the distance and the total weight of the PCD. The charged PCDs contain enough ice

to keep vaccines cool until the next recharging time point. Each health post may need more than one PCD depending upon the PCD volume and the vaccine demand (including any buffers) at the health post. The deployed PCDs remain at the health post and are allowed to be re-opened as required during the vaccination days. For lyophilized vaccines (such as Bacillus Calmette-Guerin (BCG), measles and yellow fever vaccines), open vials are discarded at the end of each immunization session. Extra PCDs are preserved at the recharging points ready to be filled with vaccines and cooling materials when they enter the deployment rotation. Recharged PCDs are brought from the recharging points to the health post and swapped out with the used PCDs. In some cases, unused vaccines left in the used PCDs are returned to the recharging points with the used PCDs. These vaccines can be restocked and sent to the health posts again.

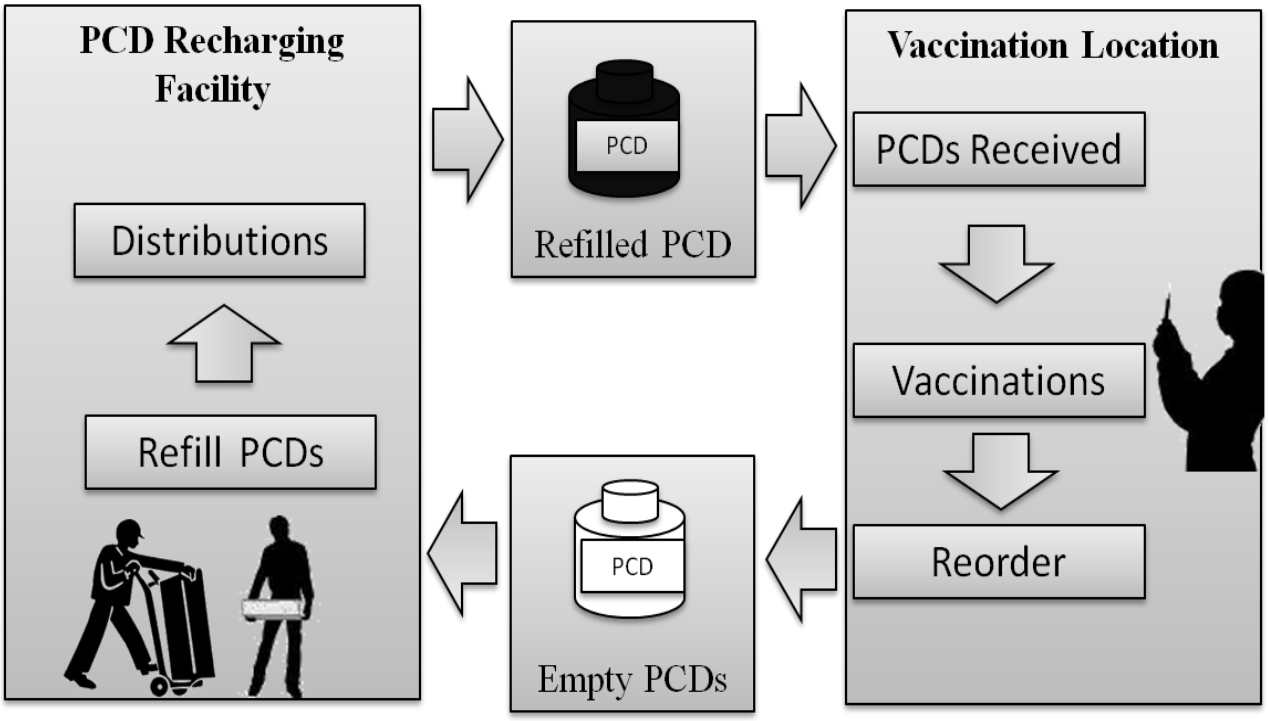

Figure 13. Passive cold device use cases

Small population catchment areas or community-base vaccination locations have relatively low volumes of vaccine demand during immunization sessions. For such cases, several locations could share a PCD while rotating the PCDs among them with a short-term stop at each location. The healthcare workers carry vaccines within the PCD to visit each vaccination point based on a pre-selected vaccination calendar. Target populations are invited to come for vaccination at specified locations during the vaccination sessions. After visiting all of the selected vaccination locations the PCD returns to the recharging point. The figure below is a schematic depiction of four vaccination points with equal demand sharing a PCD, while rotating the PCD with a one week stop at each location.

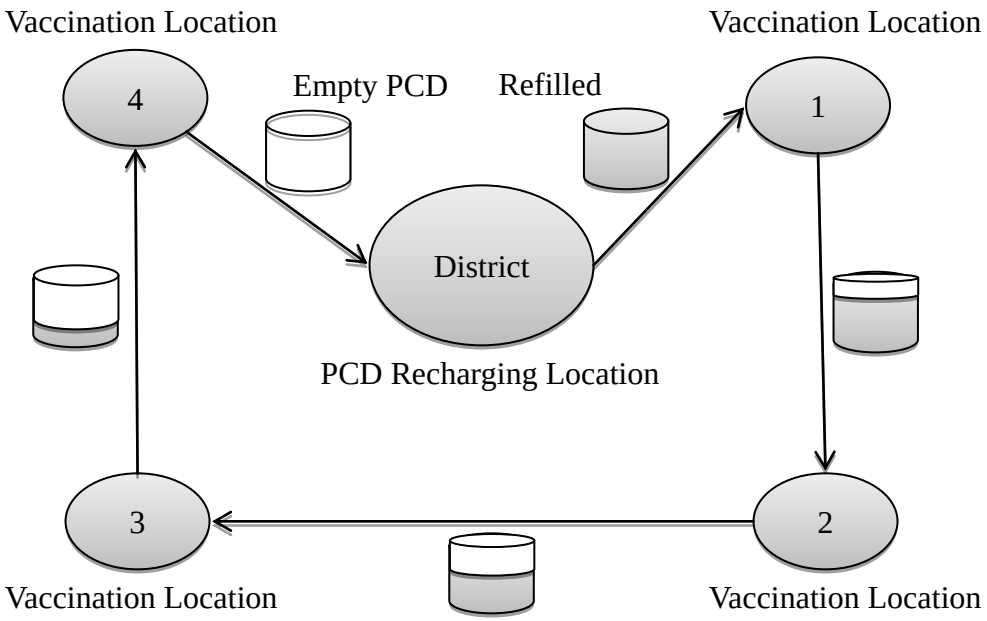

Figure 14. A PCD serves as an immunization resource for multiple communities

Use Case Options

Many competing factors influence PCD designs and configurations. To evaluate whether a particular PCD design is robust, this study verifies performance corresponding to the critical factors that change across different use cases. The key variables considered and their available options are listed below.

a. Target Population: The target population includes pregnant women and children under two years of age. The number of children of each age is computed by discounting the number of annual newborns by a mortality rate for each age. We use a growth rate of 3.63% to estimate the population in 2015 (The world factbook : Niger, 2012).

b. Vaccine Schedule: The baseline scenario considers the Expanded Program on Immunization (EPI) from the WHO. We also consider the introduction of new vaccines.

c. Replenishment Frequency: The replenishment frequency is a decision that is based on how long the PCD can keep vaccines cold and a frequency is selected that minimizes total system cost if this choice allows the PCD to fulfill vaccination needs. According to the baseline policy, each health post is assumed to receive re-filled PCDs from the recharging point every four weeks. In this study, we also investigate two-week and eight-week replenishment periods.

d. Device Rotation: Extra PCDs in the system are allocated to the recharging points. Having additional PCDs incurs additional costs but the number of additional PCDs affects the types of replenishment policies that are feasible. For example, if the device rotation ratio is 100% (i.e., the system has double the number of PCDs needed across all health posts), then all used PCDs at the health posts can be exchanged with the extra

PCDs at the same point in time. A strategy of grouping replenishments can reduce traveling distance by visiting all health points in a single route, and therefore, save on transportation costs. However, if the health posts are going to be served using multiple smaller routes then a rotation ratio of less than 100% can be employed.

e. Transportation Mode: Two transportation options are considered: the first is point-to-point shipment where all shipments are made directly from the recharging point and the second is to group all or multiple health posts into one or more shipping routes. For the direct shipping case, each health post can have a different replenishment frequency and can collect PCDs at the time when they are needed. In general, if only one or two PCDs are needed then delivery can be done using a motorcycle or 4x4 truck. For the second case, a fixed shipping schedule is more likely to be applied and all health posts would receive recharged PCDs at the same time. A larger vehicle, most likely a 4x4 truck, is required for fulfilling multiple locations' demands. Several factors need to be considered for delivery of PCDs in low and middle income countries, such as the distance, vaccine storage temperature, road conditions, commodity security, potential for driver fatigue, gas station locations and vehicle availability. Often shipping routes are planned to require a maximum of eight hours driving and avoid requiring an overnight stay.

Table 15. PCD use cases options

Factor	Options	Reference
Target population	Current population 2015 estimated	Niger census data
Vaccines	EPI EPI+NVI	(Expanded program on immunization, 2011) (Introduction of rotavirus vaccines into national immunization programmes: management manual, including operational information for health workers, 2009)
Replenishment frequency	Every 2 weeks Every 4 weeks Every 8 weeks	Niger cMYP
Extra devices for rotation	20% 50%	Assumptions
Transportation mode	Direct shipping Loop shipping*	Distances are estimated based on Niger cMYP

* Each loop contains some of the clinics served by the recharging point and multiple loops may be required. Exact loop formation decisions consider many factors including those described under Use Case Options, (e) Transportation mode.

5.3 PCD DESIGNS AND CONFIGURATIONS

PCDs are essentially designed to maintain proper temperatures to hold vaccine cool between replenishments. In order to reduce the risk of vaccine wastage due to improper storage, several points are considered when designing a PCD. For example, the PCDs are tested and the rates of heat loss under variable ambient temperatures are calculated; they include several features to access vaccines easily; they are constructed to be durable enough to withstand frequent use, etc. Furthermore, the device must be evaluated through field trials and meet WHO requirements. Elements of different PCD designs and configurations considered are as follows:

a. PCD Volume: Larger volume can provide more vaccine storage space. The drawbacks are increased cost and greater device weight. The volume also depends on the PCD internal geometry and compartment design and these factors influence the vaccine and ice packing efficiency.

b. PCD Mass: The total mass of a refilled PCD is based on the weight of the PCD itself, the vaccines placed inside of it and the ice loaded into it. The total mass impacts the flexibility associated with handling and delivering. For example, if the total mass is greater than 25 kg, then the device can only be delivered using a truck. Since hand-carried movement is the most common way of vaccine delivery at the heath post level, device weight is an important consideration. Using lighter insulation material for PCD design can reduce total mass.

c. Ice requirement: The heat leakage rate impacts the volume of ice needed to keep the required cool temperatures. Ice requirement depends on the device geometry, access point design, device materials and cooling medium.

d. Ice Buffer: Ice buffers are used to mitigate multiple risks including: variation in ambient temperature, variation in cooling media performance, frequency of device access, variation in PCD performance, and potential delays in exchanging PCDs and recharging. Ice buffers require additional space in a PCD and increase the demand for recharging freezers needed at the recharging points.

e. Hold Time (HT): Hold time measures the longest time interval that vaccines can be stored in a PCD. Heat leakage rate and cooling media provided are the primary factors that determine the HT. In general, hold time is measured using an ambient temperature assumption (one common choice is +43°C) to cover most use case situations.

5.4 MODEL DESCRIPTIONS

We develop computational models to conduct a PCD cost analysis to assess the benefits of using PCDs in the vaccine supply chain. The models can be applied to answer questions such as: (1) What is the optimal PCD design for different catchment sizes? (2) What are the benefits of efficiently routing shipments for delivering PCDs? (3) What would be the best use case for health posts to share a PCD? (4) What is the optimal replenishment frequency?

Table 16. PCD model notation

Sets of indices	
Index	*Description*
$[I]$	Index set of all vaccines, $i \in [I]$
$[J]$	Index set of all health posts, $j \in [J]$
Notation	**Description**
a^f	Annual ice recharging cost
a^n	Annual device cost
a^s	Annual transportation cost
a^t	Annual total system cost
c_j	Vaccine storage space (in liters) per PCD at health post *j* (unit: liters)
$d_{i,j}$	Demand (in doses) for vaccine *i* at health post *j*
e^k	PCD Ice buffer (%)
e^n	Extra percentage of PCDs for rotation
e^v	Vaccine buffer
f	Capacity (in liters) of ice recharging freezer
g	PCD Gross volume (in liters)
h_j	Hold time (in days) at health post *j*
k	Kilograms of ice needed to maintain PCD temperature for one week
ℓ_i	Doses per vial for vaccine *i*
v_i	Vial volume for vaccine *i*
m_j	Total mass (in kg) of a loaded PCD at health post *j*

Table 16 (continued)

n_j	Number of PCDs required at health post *j*
$o_{i,j}$	Fraction of open vial loss for vaccine *i* at health post *j*
p^b	Annual energy cost (in $) per freezer
p^f	Unit cost of ice recharging freezer
p^n	PCD Unit cost
p^s	Transportation cost (in $/km)
$q_{i,j}$	Number of vials of vaccine *i* ordered at health post *j*
r^f	Ice packing ratio for freezer
r^k	Ice packing ratio of PCD
r^v	Vaccine packing ratio of a PCD
w	Net weight (in kg) of PCD (unit: kg)
z	Maximum vehicle load (in kg)
δ	Vaccine density (in kg/cm^3)
θ_j	The number of vaccination days during a replenishment interval at health post *j*

Estimating Open Vial Waste

"Open vial waste" refers to the fact that for some vaccines, when a multi-dose vial is opened during a vaccination session, if the vial is not fully used during the vaccination session then all of the vaccine remaining in the opened vial must be discarded and cannot be used on a subsequent

vaccination day (WHO policy statement. The use of opened multi-dose vials vaccine in subsequent immunization sessions, 2012). A typical example is when a lyophilized multi-dose vaccine vial is opened and reconstituted with diluent the vaccine is only good for about six hours; after this time period the left-over vaccine doses must be discarded (Getting started with vaccine vial monitors, 2002). The amount of open vial waste depends on the vial size and the demand during a vaccination session (Lee, B. Y., et al., 2010). For example, rural areas that have a small number of children arriving for vaccination need to open more vials per vaccine demand than urban areas where the population served is larger and this results in higher open vial waste. Open vial waste (OVW) is a major consideration for the vaccination points. Estimating OVW is important to ensure that the correct amounts of vaccines are ordered and vaccine stock-outs are minimized.

Consider the demand $d_{i,j}$ of vaccine i at health post j during a vaccination session. For a single dose vial ℓ_i equals one; for multi-dose vials ℓ_i is greater than or equal to two. The OVW $o_{i,j}$ is computed as:

$$o_{i,j} = 1 - \frac{d_{i,j}}{\lceil d_{i,j}/\ell_i \rceil \ell_i} \tag{1}$$

In equation (1), the numerator of the quantity subtracted from 1 is equal to the vaccine demand during the session, and the denominator is the number of doses of vaccine made available (vials opened $\lceil d_{i,j}/\ell_i \rceil$ multiplied by vial size ℓ_i). Thus, this quantity represents the fraction of doses that are actually used, so that $o_{i,j}$ is the fraction of doses that are *not* administered to the recipients. Estimates of OVW rates are obtained by simulating vaccine demands drawn from a Poisson distribution with mean equal to the average daily demand (see

(Lee, B. Y., et al., 2010) for additional details). Values of $o_{i,j}$ for different mean demands are given in APPENDIX A.

Vaccine Ordering Quantity

To ensure that vaccines are received in correct quantities, the vaccine ordering decision involves the assessment of demand forecasts, the target population, coverage and the OVW factor. In addition, vaccine buffers are considered to avoid vaccine stock out due to random events such as shipping delays, vaccine spoilage, etc. The ordering buffer is based on the WHO guideline (Rajgopal J., et al., 2011).

The order quantity (or more precisely, the order-up-to level) $q_{i,j}$ for vaccine *i* at location *j* is computed after accounting for OVW estimates based on equation (1), and is computed via

$$q_{i,j} = \left\lceil \left\lceil \frac{\frac{\theta_j d_{i,j}}{1-o_{i,j}}}{\ell_i} \right\rceil \times (1 + e^{v}) \right\rceil \quad (2)$$

The fraction $\frac{\theta_j d_{i,j}}{1-o_{i,j}}$ is the total number of doses that must be ordered to cover demand and OVW during a replenishment interval. This quantity is divided by vial size ℓ_i and rounded up to obtain the number of vials needed. Finally, the number of vials ordered is equal to the vials needed inflated by the extra buffer, e^{v}, and rounded up again.

PCD Vaccine Storage Space

For each PCD, the vaccine storage space is the portion of the internal space available after the ice has been packed. The volume of ice is based on the hold time and the ratio of heat leakage. In general, the hold time, $h_{j,}$ at location *j* is equal to θ_j, and a linear relationship is assumed between

the hold time and the required amount of ice (with k kg required for a one week hold time). The extra ice buffer, e^k, is used to account for any stochastic variations in the hold time. The density of ice is assumed to be 0.917 kg/m3, so that after accounting for the ice packing ratio, r^k, the ice volume in liters is:

$$\frac{k\, h_j\, (1+e^k)}{0.917\, r^k} \tag{3}$$

In addition, the remaining space is discounted by the vaccine packing ratio (the fraction of storage volume in a device that can actually be occupied by vaccine vials). The vaccine storage space c_j for a device at location j is computed as:

$$c_j = r^v \left[g - \frac{k\, h_j\, (1+e^k)}{0.917\, r^k} \right] \tag{4}$$

Total Mass of a Fully-loaded PCD

The total mass, m_j, of a completely filled device used at location j is the sum of the PCD net weight, the ice weight and the vaccine weight. Given an average vaccine density of δ, this may be computed as

$$m_j = w + \frac{k\, h_j\, (1+e^k)}{r^k} + c_j \delta \tag{5}$$

The Number of PCDs Needed for a Country

In general, a single PCD type is assumed to be used for vaccine delivery in a country; this has several benefits. A single PCD type reduces initial cost and maintenance costs and from an operational standpoint, this affords more flexibility with respect to sharing or exchanging PCD parts or PCDs between different locations. The number of PCDs required for health post j is:

$$n_j = \left\lceil \frac{\sum_i v_i \, q_{i,j}}{c_j} \right\rceil \tag{6}$$

In equation (6), the vaccine order quantities $q_{i,j}$ come from equation (2) and vaccine storage space c_j comes from equation (4). The parameter e^n accounts for the extra buffer of PCDs needed for replenishment, and the additional PCDs are used to ensure that each heath post receives the re-filled PCDs at the same time that the empty PCDs are returned to the recharging locations. The total number of PCDs needed for a country is as follows:

$$N(e^k, e^n, e^v, r^k, r^v, k, g, \Theta, H, D, L, O, V) = \sum_j \left\lceil \frac{\sum_i v_i \left\lceil \left\lceil \frac{\theta_j d_{i,j}}{1-o_{i,j}} \right\rceil \times (1+e^v) \right\rceil}{r^v \left[g - \frac{k \, h_j \, (1+e^k)}{0.917 \, r^k} \right]} \right\rceil (1 + e^n) \tag{7}$$

The total number of PCDs needed in a country is the sum of the PCDs required at each health post. In equation (7), the parameters $e_k, e_n, e_v, r_k, r_v, k$ and g are applied to each health post; other parameters may be different depending on the health post populations, HT or vaccine characteristics. Θ is the vector of the number of vaccination days over a replenishment interval at the health posts, H includes all hold time settings at health posts, D is a demand matrix of vaccines i at health posts j, L is a vector of vaccine vial sizes, O is the matrix of the estimated open vial waste of vaccine i at health post j and V is a vector of the vial volumes of each vaccine i.

System Cost

The system costs include PCD costs, transportation costs and ice recharging costs. Let the PCD unit cost be p^n. We amortize the PCD cost over its useful life, assumed to be ten years of use.

With an assumed interest rate of 3%, the capital recovery factor in each year is 0.1172. Therefore, PCD annual cost a^n is:

$$a^n = 0.1172\, p^n\, N(e^k, e^n, e^v, r^k, r^v, k, g, \Theta, H, D, L, O, V) \quad (8)$$

Annual transportation cost is calculated based on the total expected distance traveled in a year between recharging points and health posts. This is multiplied by an estimated per kilometer cost, p^s, that depends on which vehicle is used for PCD delivery. The cost per kilometer is estimated based on vehicle investment, fuel, maintenance and personnel. In addition, we consider vehicle load limits. A typical motorbike used for EPI vaccine delivery has a capacity of about 15 kg in the front and 25 kg in the back. For example, if the total mass of a replenished PCD is 14 kg, then two PCDs can be carried at the same time (one on the front and one on the back). If the total mass of a PCD is great than 25 kg, then the shipment can only be done using 4x4 trucks. Assuming a maximum load of z for the mode of transportation selected. The number of annual shipments is $\frac{35}{h_j}$ for location j, the annual expected transportation cost is calculated as follows:

$$a^s = p^s \sum_j \left\lceil \frac{n_j m_j}{\mathrm{z}} \right\rceil \frac{365}{h_j} \quad (9)$$

The annual cost of recharging ice is calculated based on the recharging freezers needed, along with their maintenance and energy costs. The number of recharging freezers needed is calculated based on the ice volume needed at the health posts. Assuming a packing factor of r^f at the freezer, a useful freezer life of ten years, a 3% interest rate, (annual capital recovery factor of 0.1172), and a maintenance cost of 5% of the purchase price in each year, the total annual cost may be computed as:

$$a^f = (0.1172\, p^f + 0.05\, p^f + p^b) \left\lceil \frac{\sum_j \frac{n_j\, k\, h_j \left(1+e^k\right)}{0.917\, rf}}{f} \right\rceil \quad (10)$$

In equation (10), the first term within the parentheses is the annualized cost of the freezer purchase price, the second term is the annual maintenance cost, and the third term is the annual energy cost per freezer; the term outside the parentheses is the number of freezers needed. Finally, the total system cost is:

$$a^t = a^n + a^s + a^f \quad (11)$$

5.5 RESULTS

The analysis in this section is based on actual data from Niger to compare the economic impacts of different possible PCD designs. There are 42 district stores which recharge PCDs to service the health posts underneath them. The average number of health posts within a district is 15, ranging from 5 to 35. The model is implemented in a spreadsheet and solved numerically. The values of the PCD cost parameters for various weights, volumes and ice requirements are shown in Table 17 and Table 18. Thus, as an example, a 30 liter device that weights 12 kg and requires 2 kg of ice for a week of hold time would cost 350+750+750=$1,850. We use the cost/FIC to assess the performance of different PCD designs over a time horizon of one year. The system costs are calculated using equation (11).

Table 17. PCD costs contributions for different weight and volume combinations

Weight (kg)	Volume (Liters)	Cost parameter	
		Weight	Volume
7	10	$200	$250
7	20	$200	$750
7	30	$200	$1,250
12	20	$350	$250
12	30	$350	$750
12	40	$350	$1,250
17	30	$500	$250
17	45	$500	$750
17	60	$500	$1,250

Table 18. PCD costs contributions for different amounts of ice needed per week of hold time

Ice needed (kg/wk)	Cost parameter
1	$1,250
2	$750
3	$250

Base Case

In the base case, we considered a birth cohort of 697,637 children. The age coverage includes children under two years of age in accordance with the Niger EPI program. The vaccine target coverage is based on the GAVI plan for 2015. The hold time is set as four weeks, and this assumption is based on the current ordering policy in Niger. We use three numbers, volume-weight-ice, to present different PCD designs. The first number refers to the gross PCD volume (g), the second to its loaded mass (m), and the third to the amount of ice required to attain a hold time of 1 week (k). Table 19 shows the results of cost / FIC for different PCD designs. The blank

values indicate that the designs are infeasible because the ice requirements for the four-week hold time are greater than the gross volume of the PCD. Designs that require less ice are more cost effective because fewer PCDs are needed and there is less ice recharging cost. There is an exception when the PCD has weight 17kg and a volume of 60L. For this weight and volume configuration the 17-60-2 device has lower cost ($1.09) than the 17-60-1 ($1.11) because most health posts require one PCD and the 17-60-2 device price is cheaper than then the 17-60-1. It is also important to note that the 17-60-3 device becomes more costly than the 17-60-2 device even though the 17-60-3 has the lowest device price. While the device price plays a major role, the higher recharging ice cost impacts the overall cost performance.

The optimal PCD design corresponds to the 17-45-1 design. Most health posts require a single PCD and the PCD storage space is highly utilized. In addition, the ice recharging cost is the most inexpensive since each PCD only requires 1 kg of ice per week of hold time and a single PCD is needed at each health post.

Table 19. Cost / FIC of different PCD designs in base case

PCD weight (m)	PCD volume (g)	Ice needed (k kg/week of hold time)		
		3 kg	2 kg	1 kg
7	10			
	20			$1.33
	30		$1.72	$1.08
12	20			$1.64
	30		$1.71	$1.08
	40	$1.59	$1.23	$1.06
17	30		$1.51	$1.19
	45	$1.36	$1.10	**$1.05**
	60	$1.12	$1.09	$1.11

* Base case: hold time = 4 weeks

Impact of New Vaccines Introductions

Table 20 illustrates similar information but with the vaccine demands based on adding new vaccines to the current EPI regimen. The cost / FIC raises dramatically in the cases when the devices have small vaccine storage space (such as 7-20-1, 7-30-2, 17-20-1, 17-30-2 and 17-40-3). To satisfy the greater vaccine demands, larger PCD volumes are more desirable. As the results in Table 20 show, larger PCD volumes have less of a cost increase for the new vaccine introductions. For example, the 17-60-1 design costs $1.11 in the base case and then increases up

to $1.62 for the new vaccine introductions. This gap is much less than for small PCD designs (such as 7-20-1 which increases in cost from $1.33 to $3.35).

The variations between different designs becomes greater with new vaccine introductions, the lowest cost (17-45-1) is about three times cheaper than the highest design (7-30-2). It is also interesting that the 17-45-1 is the most inexpensive design in both the baseline and the new vaccine introduction cases.

Comparing the system costs of the three ice requirement options, the 1 kg designs are consistently lower than the 2 kg and 3 kg designs across different weight and volume settings. The 17-60-1 design becomes more inexpensive than the 17-60-2 design, as the designs requiring less ice have more vaccine storage space which is important in the case of introducing new vaccines and therefore reduces the number of PCDs needed in the system.

Table 20. Cost / FIC of different PCD designs in the new vaccine introduction case

PCD weight (m)	PCD volume (g)	Ice needed (k kg/week of hold time)		
		3 kg	2 kg	1 kg
7	10			
	20			$3.35
	30		$4.51	$2.52
12	20			$4.29
	30		$4.49	$2.52
	40	$3.23	$2.10	$1.75
17	30		$3.01	$1.99
	45	$2.56	$1.91	**$1.61**
	60	$1.90	$1.66	$1.62

Sensitivity Analysis of Different Hold Times

The purpose of this analysis is to verify if there is a robust device design for different hold time settings. The HT duration selected is related to the replenishment frequency. Ice requirements are calculated to insure that the PCD will maintain proper cooling for the duration of the time between replenishments.

Table 21. Sensitivity analysis: Different HTs for the 17-45-1 PCD

	Cost / FIC			
Parameter	**PCD cost**	**Transportation cost**	**Ice recharging cost**	**System cost**
2 weeks HT	$0.39	$1.16	$0.04	$1.60
4 weeks HT*	$0.41	$0.47	$0.06	$1.05
6 weeks HT	$0.62	$0.39	$0.12	$1.13
8 weeks HT	$0.83	$0.29	$0.19	$1.31

Table 21 **s**hows the cost summary for the 17-45-1 PCD. The PCD cost increases with the HT duration, from $0.39 (2 weeks) to $0.83 (8 weeks). PCD costs are more for longer HTs as each PCD requires more ice and has less storage space. Transportation cost is the highest for the two week HT due to more frequent shipping. There is a trade-off between transportation and ice recharging costs, the two week HT has the lowest ice recharging cost as it requires less ice volume. The system cost is the lowest when the HT is 4 weeks, and then the system cost moves up in the case of either shorter or longer HTs.

Sensitivity Analysis of PCD Costs Parameters

If the cost parameters (and hence the device price) are not known with certainty, the impact of variations in the device price with different contributions from the three design factors of weight, volume and ice requirements can be explored using sensitivity analysis. In Table 22 "regular" refers to the original value of the cost parameter for the level of the design factor in question (i.e., the corresponding value in Table 17 or Table 18), while "low" and "high" refer to where

this value is reduced or increased respectively by 50%. As an example, for the 12-30-1 device, "low," "regular," and "high" would use (respectively) values of 175, 350 and 525 for the weight cost parameter, 375, 750 and 1125 for the volume cost parameter, and 625, 1250 and 1875 for the ice requirement cost parameter.

Table 22 summarizes the most robust designs for different cost factor combinations. The 17-45-1 design is always the best when the ice requirement parameter is at the regular level and almost always the best when the parameter is at the high level. However, if this parameter is at its low value then the medium volume and medium weight device (12-30-1) becomes the best option. It is also important to note that combining changes in multiple factors impacts which design is best. One example is if the ice requirement cost parameter is at the high level and the volume cost parameter is at the low level, the 17-60-3 design is the lowest cost design.

Table 22. Optimal PCD designs

Weight parameter	Volume parameter	Ice requirement parameter		
		Low (-50%)	Regular	High (+50%)
Low (-50%)	Low (-50%)	12-30-1	17-45-1	17-60-3
	Regular	12-30-1	17-45-1	17-45-1
	High (+50%)	12-30-1	17-45-1	17-45-1
Regular	Low (-50%)	12-30-1	17-45-1	17-60-3
	Regular	12-30-1	17-45-1	17-45-1
	High (+50%)	12-30-1	17-45-1	17-45-1
High (+50%)	Low (-50%)	12-30-1	17-45-1	17-60-3
	Regular	12-30-1	17-45-1	17-45-1
	High (+50%)	12-30-1	17-45-1	17-45-1

Because the cost of different PCD features may vary from those stated in Table 18 and Table 19, we perform a sensitivity analysis to determine if there is a design that is robust to cost variation. This approach evaluates each of the three PCD designs given in Table 22 across each of the 27 scenarios in the table to determine how far each design deviates from the optimal solution for each scenario. Table 23, Table 24 and Table 25 report the cost deviations of the 12-30-1, 17-45-1 and 17-60-3 PCDs, respectively from the optimal design for each of the 27 cost scenarios. The percentage represents how much the design deviates from the optimal device cost. For the 12-30-1 design, Table 23 shows zero deviation in the low-cost (-50%) ice requirement cases, about 2% to 3% cost deviations for the regular-cost ice requirement and the worst cases occur at the high-cost ice requirement, which has cost deviations as high as 14%. Similarly, we found the worst case for the 17-45-1 PCD is about a 5% deviation from the optimal design, and about 19% deviation for the 17-60-3 PCD. Different robustness criteria can be used to determine the overall most robust solution and two of the most common criteria are the average regret and minmax regret. Average regret is the average deviation from the optimal solution for each scenario. Minmax regret evaluates the maximum deviation from the optimum solution across all scenarios and prefers the solution that minimizes the maximum deviation (Kouvelis, P. and Yu, G., 1997).The 17-45-1 PCD is the most robust solution with regard to cost parameter variations using both of these criteria because its average regret is 1% compared to 4% for the 12-30-1 design and 8% for the 17-60-3 design and its maximum regret is 5% compared to 14% for the 12-30-1 design and 19% for the 17-60-3 design.

Table 23. The 12-30-1 design cost deviations from the best design

Weight parameter	Volume parameter	Ice requirement parameter		
		Low (-50%)	Regular	High (+50%)
Low (-50%)	Low (-50%)	0%	2%	13%
	Regular	0%	2%	7%
	High (+50%)	0%	3%	7%
Regular	Low (-50%)	0%	2%	13%
	Regular	0%	3%	7%
	High (+50%)	0%	3%	7%
High (+50%)	Low (-50%)	0%	2%	14%
	Regular	0%	3%	7%
	High (+50%)	0%	3%	7%

Table 24. The 17-45-1 design cost deviations from the best design

Weight parameter	Volume parameter	Ice requirement parameter		
		Low (-50%)	Regular	High (+50%)
Low (-50%)	Low (-50%)	5%	0%	5%
	Regular	4%	0%	0%
	High (+50%)	1%	0%	0%
Regular	Low (-50%)	4%	0%	5%
	Regular	2%	0%	0%
	High (+50%)	1%	0%	0%
High (+50%)	Low (-50%)	4%	0%	5%
	Regular	3%	0%	0%
	High (+50%)	1%	0%	0%

Table 25. The 17-60-3 design cost deviations from the best design

Weight parameter	Volume parameter	Ice requirement parameter		
		Low (-50%)	Regular	High (+50%)
Low (-50%)	Low (-50%)	15%	1%	0%
	Regular	13%	7%	0%
	High (+50%)	13%	11%	4%
Regular	Low (-50%)	13%	2%	0%
	Regular	18%	7%	0%
	High (+50%)	19%	10%	5%
High (+50%)	Low (-50%)	13%	2%	0%
	Regular	18%	7%	1%
	High (+50%)	19%	10%	5%

Generalization of PCD Designs

It has been noted in the previous discussion that many parameters affect PCD design and cost performance. Uncertainty about the population demand is one of the main factors affecting PCD design. This led to an additional analysis based on changing the population demand to determine how it affects the choice of PCD design. The annual birth cohort was set at levels of 500, 1000, 1500, 2000, 2500, and 3000. For each level, we assumed there were 16 health posts serving an annual birth cohort of that size within one district location. Two vaccine schedules were tested – the current Niger EPI schedule and with the introduction of Rotavirus and Pneumococcal vaccines. Table 26 lists the optimal PCD designs for the six different catchment size areas for both vaccine schedules. For the smallest catchment size area (i.e., 500 annual births at each IHC), 12-30-1 is the most cost effective design in the EPI only case, and 12-40-1 is the best design for the new vaccine introductions. For the medium catchment size areas (i.e., annual

births are either 1000 or 2000), the best designs are 17-45-1 and 17-45-2 (where 17-45-1 is also the best design in Niger). For the larger catchment size areas the larger designs perform better and the 17-60-1 design is the optimal design in both the base EPI and new vaccine introduction cases when there are 3,000 annual births.

Table 26. Optimal PCD designs for different catchment sizes

Annual birth per IHC	Vaccine	
	EPI	New vaccine introduction
500	12-30-1	12-40-1
1,000	17-45-2	17-45-1
1,500	12-40-1	17-60-2
2,000	17-45-1	17-45-1
2,500	17-60-2	17-60-1
3,000	17-60-1	17-60-1

The volume of the optimal design increases as the catchment area size increases, so it may be best to use multiple sizes for a country that has health posts with very different catchment size areas. APPENDIX C has the details of a robustness analysis based on catchment size area (similar to that done for Niger). For small catchment areas (500 annual births) the most robust design is the 12-30-1 design at the EPI case and 12-40-1 at the new vaccine introduction case. The 17-45-1 design (which was the most robust device in Niger) is the best choice for medium size catchment areas (1,000 to 2,000 annual births). The 17-60-1 design is the most robust for larger catchment areas (2,500 or 3,000 annual births). Such analysis could easily be extended to other ranges of catchment sizes and help to identify the best designs for those use cases.

5.6 CONCLUSIONS

In this study, we develop a computational model to evaluate different PCD designs for vaccine distribution for various use cases. We provide an example to demonstrate how PCDs can be used to deliver and store vaccines in Niger. The cost analysis provides information to understand the benefits of using PCDs. Our sensitivity analysis identifies a robust design for the situation when device price cannot be known with accuracy. Similar analysis can be conducted for deviations of either transport cost or ice recharging cost. Our general model provides the required resources and their associated costs for vaccine transportation and storage. The model can be readily populated and re-used for other countries, which is useful for vaccine logistics and economic modelers to assess the cost-effectiveness of PCDs.

There are limitations to this study. We examined the cost tradeoffs in changing either PCD volume or the ice needed per week of HT parameters, in the absence of changing the weight parameter. This is because there is no cost penalty associated with device weight, and therefore heavy, but low price, designs are always the best choice. However, in real life device weight must be considered and its impacts on logistics system design, particularly aspects of loading / unloading operations, vehicle maximum loads, and how device portability affects outreach vaccinations. Reasonable design considerations may include that at most 25 kilogram may be moved by a person, a 50 kilogram device would require two people, and a device of more than 50 kilograms would be primarily stationary and could not be used for outreach activities.

6.0 RESEARCH SUMMARY AND FUTURE DIRECTIONS

The enormous economic impact of diseases has drawn global attention. Controlling diseases is one of the highest priorities in healthcare decision making. While improvements in medical/pharmacy technologies have significantly improved the quality of life and extended life expectancy in many parts of the world, resource shortages and effective use of existing resource budgets are still major issues in low and middle income countries (The children's vaccine initiative: continuing activities, 1995). Intervention policies must consider both costs and health outcomes. This study draws upon domain knowledge in various fields ranging from medicine, epidemiology, sociology and industrial engineering to build models and quantitatively analyze various systems relevant to vaccine delivery and logistics so as make decisions that will help improve health outcomes.

6.1 RESEARCH SUMMARY

This research has focused on three major areas. First, we have presented the development of a mathematical model for the vaccine supply chain in low and middle income countries. The model has been used to analyze vaccine policies and results have been reported here and in (Lee, B. Y., et al., 2012). To our knowledge, this is the first mathematical programming model for a generic WHO-EPI vaccine distribution network. The value of such a model stems from the fact that there are many inefficiencies in existing distribution networks and public health officials and policy makers can use the model as a planning tool. It can be used to better understand

bottlenecks and resource constraints in existing networks so as to improve vaccine delivery and immunization rates. In addition, it can also be used to evaluate several types of interventions and changes or updates in policy; this was illustrated by the four different scenarios for Niger described in Chapter 3. Versions of the model have already been applied to other countries including Thailand and Vietnam.

A second research focus that was centered on linking the mathematical programming model with a disease propagation model extends the application of quantitative approaches to assess the benefits of vaccination policies. The disease propagation model was an extension of a stochastic disease model based on the published model of Ferrari et al. (Ferrari, M. J., et al., 2008) and utilizes real world data from Niger. To assess the interactions between disease dynamics and supply chain decisions, we present a framework for linking the disease and supply chain models. The framework can be applied to assess the performance of vaccination policies by providing realistic disease propagation estimates for a specific country. The framework also lets decision makers understand how supply chain decisions may impact disease outcomes.

Finally, we explored the use of passive cold devices (PCDs) to support immunization activities. We develop and present a cost model which includes factors that are critical to PCD operations. The model was applied to identify the most robust PCD design from various options using realistic data about features, performance and cost.

Overall, this dissertation includes several studies related to vaccine supply chains. The major contributions are listed below.

- Development of a mixed integer linear programming model for the vaccine supply chain in low and middle-income countries.

- Application of the mixed integer linear programming model to answer vaccine policy questions based on real world data and actual health policy concerns.
- Identification of bottlenecks in existing supply chains and development of alternatives for supply chain adjustments to address these bottlenecks.
- Development of a framework for linking disease and supply chain models, and application of the framework to assess vaccination strategy effectiveness using the metric of infections averted, along with an identification of resources needed.
- Investigation of alternative passive cold device designs and identification of the most robust designs for real world applications.
- Robust analyses to assess the interactions between passive cold device designs and supply chain policies.

6.2 FUTURE DIRECTIONS

To support vaccine dissemination around the world, we plan to extend the work described here to other Global Alliance for Vaccines and Immunization (GAVI) eligible countries. The anticipated analyses will use models such as the ones described herein to address issues associated with vaccine policies. In addition there are several interesting topics that can be investigated in future work.

- In our present model, the transportation mode for vaccine delivery is point-to-point shipping; we plan to consider details of route shipping as an extension. We have developed an initial approach using a sweep vehicle routing algorithm. This approach determines routing and

sequencing that attempt to minimize total travel distance. In the future, we plan to study this further and improve the efficiency of this approach in terms of solution quality.

- Exploring simultaneous interactions between disease propagation and the supply chain is an interesting topic to pursue. During a disease outbreak, it may be necessary to make unexpected changes to the vaccine distribution plan to respond to the outbreak. Assessments of which changes to make can be conducted via a real-time link between the disease and supply chain models. A feedback loop could exchange information between the two systems so that vaccine distribution decisions can be changed dynamically in order to mitigate the spread of disease. For example, a ring vaccination policy could be used to vaccinate the populations that are most likely to contact infected individuals once an outbreak occurs. If the distribution network is not capable of delivering vaccines to the outbreak areas in a timely manner, then the disease can spread more widely and affect other communities. The distribution strategy in the next time step needs to be adjusted according to where the new infections are occurring. It is expected that the simultaneous sharing of outbreak and supply chain information for decision making can significantly improve the performance of disease response plans. However, this also entails significant challenges from the viewpoint of integrating the computer codes for the two models.
- PCD replenishment frequency: Decisions about PCD replenishment frequency depend on vaccine demands, transportation, storage, ice recharging, etc. There is a trade-off between transportation cost, storage cost and ice recharging cost. For example, more frequent shipping could reduce device and ice recharging costs, however, it will have higher transportation cost. The purpose of this study would be to determine a PCD replenishment

frequency that minimizes the overall system cost and helps to identify the best hold time duration for deploying PCDs in a country.

- Cold chain applications: Similar to vaccines, other products such as, blood/organ delivery, food and perishable commodities are also required to be kept in cool temperatures. The problems of delivering these items exist in both developed and low and middle income country. We anticipate applying our knowledge of the vaccine supply chain to other cold chains.

APPENDIX A

OPEN VIAL WASTE ESTIMATION

Table A-1 shows how the percentage of doses wasted varies with the average daily demand and vial size. Open vial waste is estimated by using a simulation which draws daily demand from a Poisson distribution, and the open vial waste percentage for each scenario is the average of 1000 simulation trials.

Table A - 1. Open vial waste by average daily demand at a clinic and doses per vial

Average daily demand	Vial size 10	Vial size 20	Average daily demand	Vial size 10	Vial size 20	Average daily demand	Vial size 10	Vial size 20
1	0.8418	0.9209	41	0.0989	0.1874	81	0.0526	0.1047
2	0.7687	0.8843	42	0.0968	0.1877	82	0.0520	0.1039
3	0.6844	0.8421	43	0.0947	0.1874	83	0.0514	0.1031
4	0.5937	0.7963	44	0.0928	0.1862	84	0.0508	0.1022
5	0.5035	0.7483	45	0.0909	0.1841	85	0.0503	0.1013
6	0.4232	0.6993	46	0.0891	0.1811	86	0.0497	0.1003
7	0.3623	0.6497	47	0.0874	0.1772	87	0.0492	0.0993
8	0.3243	0.5999	48	0.0857	0.1728	88	0.0486	0.0982
9	0.3047	0.5501	49	0.0841	0.1679	89	0.0481	0.0970
10	0.2950	0.5008	50	0.0826	0.1628	90	0.0476	0.0959
11	0.2879	0.4525	51	0.0811	0.1578	91	0.0471	0.0947
12	0.2790	0.4069	52	0.0796	0.1531	92	0.0466	0.0936
13	0.2669	0.3659	53	0.0783	0.1488	93	0.0462	0.0925
14	0.2523	0.3320	54	0.0769	0.1451	94	0.0457	0.0915
15	0.2365	0.3075	55	0.0756	0.1421	95	0.0452	0.0905
16	0.2214	0.2932	56	0.0744	0.1397	96	0.0448	0.0896
17	0.2081	0.2884	57	0.0732	0.1378	97	0.0443	0.0887
18	0.1972	0.2909	58	0.0720	0.1365	98	0.0439	0.0879
19	0.1886	0.2978	59	0.0709	0.1355	99	0.0435	0.0872
20	0.1815	0.3060	60	0.0698	0.1348	100	0.0431	0.0865
21	0.1755	0.3133	61	0.0687	0.1341	101	0.0427	0.0858
22	0.1699	0.3182	62	0.0677	0.1334	102	0.0423	0.0852
23	0.1644	0.3197	63	0.0667	0.1326	103	0.0419	0.0845
24	0.1588	0.3175	64	0.0657	0.1315	104	0.0415	0.0839
25	0.1533	0.3119	65	0.0647	0.1302	105	0.0411	0.0832
26	0.1480	0.3031	66	0.0638	0.1287	106	0.0407	0.0825
27	0.1429	0.2916	67	0.0629	0.1269	107	0.0404	0.0818
28	0.1383	0.2782	68	0.0621	0.1249	108	0.0400	0.0811
29	0.1340	0.2637	69	0.0612	0.1228	109	0.0396	0.0804
30	0.1302	0.2489	70	0.0604	0.1206	110	0.0393	0.0796
31	0.1266	0.2345	71	0.0596	0.1185	111	0.0390	0.0789
32	0.1232	0.2213	72	0.0588	0.1164	112	0.0386	0.0782
33	0.1200	0.2099	73	0.0581	0.1144	113	0.0383	0.0775
34	0.1170	0.2007	74	0.0573	0.1126	114	0.0380	0.0768
35	0.1140	0.1938	75	0.0566	0.1110	115	0.0377	0.0762
36	0.1112	0.1893	76	0.0559	0.1095	116	0.0373	0.0756
37	0.1085	0.1868	77	0.0552	0.1083	117	0.0370	0.0749
38	0.1059	0.1858	78	0.0545	0.1072	118	0.0367	0.0744
39	0.1034	0.1860	79	0.0539	0.1063	119	0.0364	0.0738
40	0.1011	0.1866	80	0.0533	0.1055	120	0.0361	0.0733

APPENDIX B

STOCHASTIC DISEASE MODEL SIMULATION RESULTS

The Table B - 1 shows the individual simulation replication results for estimating disease incidence that are summarized in Table 11. Similarly, Table B - 2 shows in the individual simulation replication results for the data summarized in Table 13, and Table B - 3, Table B - 4, Table B - 5, Table B - 6 and Table B - 7 contain similar data for the results that are summarized in Table 14.

Table B - 1. Simulated monthly cases per 100,000 for different vaccination policies

Replication ID	RI only	Supply chain capacities shared for RI and SIA	SIA does not share supply chain capacities with RI
1	23.5138	20.6738	20.0734
2	22.5719	20.4374	19.3092
3	24.3651	21.3654	19.8108
4	22.7460	20.3648	18.5814
5	23.9047	19.7348	18.5286
6	24.6955	20.9319	20.5350
7	22.6254	19.8079	20.3760
8	23.2487	20.5849	19.2516
9	23.1185	21.1134	18.4840
10	24.9085	19.9256	20.7450
Standard deviation	0.8615	0.5543	0.8617
Mean	23.5698	20.4940	19.5695

Table B - 2. Simulated monthly cases per 100,000 for the reinforced supply chain scenarios

Replication ID	RI only	RI and SIA
1	15.9200	14.1044
2	17.0652	13.8432
3	16.8958	13.5151
4	17.2444	14.6953
5	15.5117	14.4090
6	17.5916	14.4647
7	15.8456	14.1601
8	16.4097	13.2621
9	16.0053	13.7812
10	17.3759	15.2112
Standard deviation	0.7006	0.5786
Mean	16.5887	14.1446

Table B - 3. Simulated monthly cases per 100,000 for RI visit rate between 78% and 82%

Replication ID	Cumulative RI visit rate				
	78%	**79%**	**80%**	**81%**	**82%**
1	15.9200	12.3733	8.0397	5.6056	1.8745
2	17.0652	11.0745	6.8666	5.0120	1.9698
3	16.8958	12.6340	8.1583	5.8061	3.2651
4	17.2444	11.0745	6.8666	5.0140	1.9698
5	15.5117	12.6340	8.1583	5.8061	3.2651
6	17.5916	12.0239	8.1246	5.3270	2.8325
7	15.8456	12.1165	8.0602	5.7435	2.2017
8	16.4097	12.0419	7.8558	5.2849	2.2282
9	16.0053	11.4941	7.3853	5.3175	1.9683
10	17.3759	11.3247	8.0767	5.4063	3.1131
Standard deviation	0.7385	0.5998	0.5233	0.2990	0.5818
Mean	16.5865	11.8791	7.7592	5.4323	2.4688

Table B - 4. Simulated monthly cases per 100,000 for RI visit rate between 83% and 87%

Replication ID	Cumulative RI visit rate				
	83%	**84%**	**85%**	**86%**	**87%**
1	0.8018	0.0949	0.0583	0.0221	0.0019
2	1.7343	0.1022	0.0036	0.0088	0.0067
3	0.5343	0.0344	0.0403	0.0456	0.0149
4	1.7343	0.1022	0.0036	0.0088	0.0067
5	0.5343	0.0354	0.0403	0.0456	0.0149
6	1.1856	0.0357	0.0439	0.0080	0.0120
7	1.0429	0.0931	0.0022	0.0439	0.0133
8	0.9844	0.0764	0.0554	0.0438	0.0067
9	0.9071	0.0365	0.0241	0.0278	0.0040
10	1.5591	0.0450	0.0245	0.0080	0.0148
Standard deviation	0.4479	0.0306	0.0213	0.0172	0.0049
Mean	1.1018	0.0656	0.0296	0.0262	0.0096

Table B - 5. Simulated monthly cases per 100,000 for RI visit rate between 88% and 100%

Replication ID	Cumulative RI visit rate				
	88%	**89%**	**90%**	**95%**	**100%**
1	0.0062	0.0090	0.0081	0.0032	0.0008
2	0.0134	0.0100	0.0019	0.0044	0.0007
3	0.0169	0.0049	0.0044	0.0030	0.0006
4	0.0134	0.0100	0.0019	0.0044	0.0007
5	0.0169	0.0049	0.0044	0.0030	0.0006
6	0.0166	0.0065	0.0051	0.0032	0.0007
7	0.0099	0.0064	0.0012	0.0039	0.0007
8	0.0156	0.0088	0.0062	0.0037	0.0008
9	0.0154	0.0080	0.0029	0.0037	0.0007
10	0.0102	0.0095	0.0051	0.0038	0.0007
Standard deviation	0.0036	0.0020	0.0022	0.0005	0.0001
Mean	0.0134	0.0078	0.0041	0.0036	0.0007

Table B - 6. Simulated monthly cases per 100,000 for SIA visit rate between 7% and 50%

Replication ID	SIA visit rate					
	7%	**15%**	**20%**	**30%**	**40%**	**50%**
1	14.1044	8.8328	8.6986	1.8952	0.7443	0.2465
2	13.8432	9.6615	6.8561	2.4928	0.4896	0.5418
3	13.5151	10.0040	0.4876	3.9088	0.3644	0.2146
4	14.6953	8.8705	4.3230	0.5998	0.9741	0.2803
5	14.4090	8.4933	7.6031	0.9696	0.5875	0.5087
6	14.4647	10.9811	6.5144	0.8979	0.5387	0.4841
7	14.1601	10.8706	9.5143	2.7604	0.1249	0.6575
8	13.2621	9.8210	7.5175	1.3050	0.0681	0.0405
9	13.7812	10.9107	6.8514	3.6859	1.8418	0.1046
10	15.2112	10.0163	6.8432	5.7120	0.6294	0.2207
Standard deviation	0.5786	0.9049	2.5260	1.6340	0.5023	0.2047
Mean	14.1446	9.8462	6.5209	2.4227	0.6363	0.3299

Table B - 7. Simulated monthly cases per 100,000 for SIA visit rate between 60% and 100%

Replication ID	SIA visit rate				
	60%	**70%**	**80%**	**90%**	**100%**
1	0.0516	0.1661	0.2475	0.0444	0.0097
2	0.3968	0.2209	0.1158	0.1178	0.0464
3	0.0391	0.0856	0.2184	0.0515	0.0132
4	0.4584	0.0818	0.1555	0.0039	0.0764
5	0.1463	0.0393	0.0701	0.0816	0.1269
6	0.0938	0.0172	0.1522	0.0847	0.0457
7	0.4936	0.3868	0.1954	0.0669	0.0891
8	0.2041	0.4174	0.0574	0.1530	0.0364
9	0.2378	0.6280	0.1391	0.0067	0.0991
10	0.2669	0.0178	0.0191	0.1048	0.0702
Standard deviation	0.1649	0.2071	0.0730	0.0473	0.0378
Mean	0.2388	0.2061	0.1370	0.0715	0.0613

APPENDIX C

COST PERFORMANCE OF PCD DESIGNS

Table C - 1, Table C - 2 and Table C - 3 present the cost performance data that is used for identifying robust device designs and the cost deviations shown in Table 23, Table 24 and Table 25.

Table C - 1. Cost performance for the 12-30-1 design

PCD weight (m)	PCD volume (g)	Ice needed (k kg/week of hold time)		
		-50%	Regular	+50%
-50%	-50%	$0.81	$0.95	$1.08
	Regular	$0.82	$1.07	$1.21
	+50%	$1.07	$1.20	$1.34
Med	-50%	$0.82	$0.95	$1.08
	Regular	$0.94	$1.08	$1.21
	+50%	$1.07	$1.20	$1.34
+50%	-50%	$0.82	$0.95	$1.09
	Regular	$0.94	$1.08	$1.21
	+50%	$1.07	$1.20	$1.34

Table C - 2. Cost performance for the 17-45-1 design

PCD weight (*m*)	PCD volume (*g*)	Ice needed (*k* kg/week of hold time)		
		-50%	Regular	+50%
-50%	-50%	$0.85	$0.93	$1.01
	Regular	$0.85	$1.05	$1.13
	+50%	$1.08	$1.16	$1.25
Med	-50%	$0.85	$0.93	$1.01
	Regular	$0.96	$1.05	$1.13
	+50%	$1.08	$1.17	$1.25
+50%	-50%	$0.85	$0.93	$1.01
	Regular	$0.97	$1.05	$1.13
	+50%	$1.08	$1.17	$1.25

Table C - 3. Cost performance for the 17-60-3 design

PCD weight (*m*)	PCD volume (*g*)	Ice needed (*k* kg/week of hold time)		
		-50%	Regular	+50%
-50%	-50%	$0.93	$0.94	$0.96
	Regular	$0.93	$1.12	$1.13
	+50%	$1.21	$1.29	$1.30
Med	-50%	$0.93	$0.95	$0.96
	Regular	$1.11	$1.12	$1.13
	+50%	$1.27	$1.29	$1.31
+50%	-50%	$0.93	$0.95	$0.96
	Regular	$1.11	$1.12	$1.14
	+50%	$1.27	$1.29	$1.31

The following tables provide cost performance data for the sensitivity analysis regarding different numbers of annual births that is presented in Table 26. Table C - 4 contains data for the cost performance for different annual births in the EPI vaccine case, and Table C - 5 is for the new vaccine introduction case.

Table C - 4. Cost performance for different annual births in the EPI vaccine scenario

Annual births	PCD design					
	12-30-1	12-40-1	17-45-2	17-45-1	17-60-2	17-60-1
500	$1.47	$2.23	$2.23	$2.28	$2.40	$2.46
1000	$1.43	$1.12	$1.11	$1.14	$1.20	$1.23
1500	$0.95	$0.74	$1.04	$0.76	$0.80	$0.82
2000	$0.71	$0.78	$0.78	$0.57	$0.60	$0.61
2500	$0.57	$0.62	$0.62	$0.64	$0.48	$0.49
3000	$0.71	$0.52	$0.52	$0.54	$0.58	$0.41

Table C - 5. Cost performance for different annual births in the new vaccine introduction scenario

Annual births	Optimal PCD design					
	12-30-1	12-40-1	17-45-2	17-45-1	17-60-2	17-60-1
500	$4.23	$3.12	$3.99	$3.22	$3.45	$2.46
1000	$2.81	$2.00	$2.00	$1.61	$1.73	$1.23
1500	$1.87	$1.33	$1.63	$1.39	$1.15	$0.82
2000	$2.10	$1.22	$1.44	$1.04	$1.13	$0.61
2500	$1.95	$1.15	$1.15	$1.02	$1.11	$0.49
3000	$1.63	$0.96	$1.11	$0.85	$0.93	$0.41

Six different PCD designs perform the best across the twelve scenarios (six annual birth levels and two sets of vaccines) and their cost data is in Table C - 4 and Table C - 5. The following tables provide cost performance data for the sensitivity analysis regarding different numbers of annual births that is presented in Table 26. This approach evaluates how far each of the six PCD designs deviates from the optimal solution for each scenario. Table C - 6, Table C – 7, Table C - 8, Table C - 9, Table C - 10 and Table C - 11 report the cost deviations from the optimal design for each of the different annual birth scenarios. There is no one design that is optimal across all of the annual birth and vaccine schedule combinations. The 17-60-1 design has the overall lowest average deviation but has a maximum deviation of 67% for the 500 annual births and EPI vaccines case. In fact, each design has a maximum deviation of 52% or higher. Thus, it appears that different annual birth sizes are best served by different PCD designs. For small annual births (500) the 12-30-1 design has the lowest costs for the EPI schedule and with new vaccine introductions is 36% above the optimal cost (where 12-40-1 is the optimal design). The 12-30-1 design has the best average performance and the best worst case performance across the 500 annual birth scenarios. For medium annual births (1000-2000) the 17-45-1 design has the lowest average deviation (4%), but has a maximum deviation of 21% for the 1500 annual births and new vaccine introduction case (where 17-60-2 is the optimal design). The 17-60-2 design has a lower maximum regret, 8%, but has a higher average deviation (6%). The 17-45-1 and 17-60-2 perform similarly for medium annual births but we give a slight advantage to the 17-45-1 design since it has a lower average deviation. For large annual births (2500-3000) the 17-60-1 design is the most robust design for both the EPI vaccines and new vaccine introduction cases, because its average regret and maximum regret are the lowest among the six designs.

Table C - 6. Cost deviation for different catchment size locations for the 12-30-1 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	12-30-1 Cost	Deviation	Optimal PCD Cost	12-30-1 Cost	Deviation
500	$1.47	$1.47	0%	$3.12	$4.23	36%
1000	$1.11	$1.43	28%	$1.61	$2.81	74%
1500	$0.74	$0.95	28%	$1.15	$1.87	63%
2000	$0.57	$0.71	25%	$1.04	$2.10	101%
2500	$0.48	$0.57	19%	$0.94	$1.95	109%
3000	$0.41	$0.71	72%	$0.78	$1.63	109%

Table C - 7. Cost deviation for different catchment size locations for the 12-40-1 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	12-40-1 Cost	Deviation	Optimal PCD Cost	12-40-1 Cost	Deviation
500	$1.47	$2.23	52%	$3.12	$3.12	0%
1000	$1.11	$1.12	0%	$1.61	$2.00	24%
1500	$0.74	$0.74	0%	$1.15	$1.33	16%
2000	$0.57	$0.78	36%	$1.04	$1.22	17%
2500	$0.48	$0.62	30%	$0.94	$1.15	23%
3000	$0.41	$0.52	27%	$0.78	$0.96	23%

Table C - 8. Cost deviation for different catchment size locations for the 17-45-2 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	17-45-2 Cost	Deviation	Optimal PCD Cost	17-45-2 Cost	Deviation
500	$1.47	$2.23	52%	$3.12	$3.99	28%
1000	$1.11	$1.11	0%	$1.61	$2.00	24%
1500	$0.74	$1.04	39%	$1.15	$1.63	41%
2000	$0.57	$0.78	36%	$1.04	$1.44	38%
2500	$0.48	$0.62	30%	$0.94	$1.15	23%
3000	$0.41	$0.52	27%	$0.78	$1.11	42%

Table C - 9. Cost deviation for different catchment size locations for the 17-45-1 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	17-45-1 Cost	Deviation	Optimal PCD Cost	17-45-1 Cost	Deviation
500	$1.47	$2.28	56%	$3.12	$3.22	3%
1000	$1.11	$1.14	3%	$1.61	$1.61	0%
1500	$0.74	$0.76	2%	$1.15	$1.39	21%
2000	$0.57	$0.57	0%	$1.04	$1.04	0%
2500	$0.48	$0.64	34%	$0.94	$1.02	9%
3000	$0.41	$0.54	31%	$0.78	$0.85	9%

Table C - 10. Cost deviation for different catchment size locations for the 17-60-2 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	17-60-2 Cost	Deviation	Optimal PCD Cost	17-60-2 Cost	Deviation
500	$1.47	$2.40	63%	$3.12	$3.45	11%
1000	$1.11	$1.20	8%	$1.61	$1.73	7%
1500	$0.74	$0.80	8%	$1.15	$1.15	0%
2000	$0.57	$0.60	5%	$1.04	$1.13	8%
2500	$0.48	$0.48	0%	$0.94	$1.11	19%
3000	$0.41	$0.58	41%	$0.78	$0.93	19%

Table C - 11. Cost deviation for different catchment size locations for the 17-60-1 PCD

Annual birth	EPI			New vaccine introduction		
	Optimal PCD Cost	17-60-1 Cost	Deviation	Optimal PCD Cost	17-60-1 Cost	Deviation
500	$1.47	$2.46	67%	$3.12	$3.57	14%
1000	$1.11	$1.23	10%	$1.61	$1.78	11%
1500	$0.74	$0.82	10%	$1.15	$1.19	3%
2000	$0.57	$0.61	7%	$1.04	$1.17	12%
2500	$0.48	$0.49	2%	$0.94	$0.94	0%
3000	$0.41	$0.41	0%	$0.78	$0.78	0%

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