IMPACTS OF VACCINE COLD CHAIN LOGISTICS ON VACCINE EPIDEMIOLOGY

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Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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The performance of vaccine logistics systems (i.e., the steps in a supply chain necessary to get vaccines from manufacturers to patients) can impact whether vaccines are delivered at the right time, place and in the right condition for patients during immunization sessions. Immunization coverage in a population depends on a well-functioning vaccine supply chain. If target populations are not immunized before exposure, they are left unprotected against vaccine preventable diseases (VPD's) and can contribute to infectious disease transmission in their communities.

Changes may be made to logistics systems without considering their potential effects on vaccine distribution and availability at vaccinating health centers. The combined works of this dissertation illustrate such changes and resulting impacts on vaccine availability, including: changes to vaccine presentations, changes to the vaccine supply chain structure, and changes to a vaccine regimen.

The Vaccine Modeling Initiative (VMI) developed the Highly Extensible Resource for Modeling Supply chains (HERMES), a stochastic, discrete-event simulation model. VMI collected information on vaccine cold chain equipment (e.g., refrigerators and freezers), transportation fleets, demographic indicators for target populations, and supply chain operating policies (e.g., shipping frequencies) for the country Niger and for Trang province in Southern

Thailand. HERMES was then used to evaluate various supply chain interventions and determine their impacts on logistics indicators including: vaccine availability at health centers, transportation and storage utilization, and additional capacity requirements.

With over a dozen new vaccines being introduced into national immunization programs in the next decade, logistics systems will be further pressed to ensure vaccines are delivered to their target populations. These studies will highlight the importance of considering vaccine logistics systems when making changes to immunization programs, and suggest potential alternative strategies to improve the performance of supply chains and ultimately vaccination coverage rates. Furthermore, these studies will demonstrate the utility in using computational models to evaluate and provide solutions for public health challenges by representing relationships that would not otherwise be apparent.

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PREFACE

I owe my deepest gratitude to Dr. Lee for his mentorship and support throughout my doctoral studies at the University of Pittsburgh. His guidance has been invaluable to my successful completion of this degree and to my journey in becoming an independent thinker. I would also like to thank my doctoral committee; Dr. Brown, Dr. Norman, Dr. Rajgopal, and Dr. Wisniewski for their time, continuous support, and for imparting knowledge from their respective backgrounds. It has been an honor working with each of them. To the members of the Vaccine Modeling Initiative Logistics team, especially Joel Welling, Rachel Bailey, Sheng-I Chen, Diana Connor, and Angela Wateska, thank you. I have enjoyed getting to know, working with and learning from them, and I consider them all dear friends. They have transformed what might have been an arduous process into an exciting and intellectually stimulating experience. Finally, and most importantly, I would like to thank my friends and colleagues from the Graduate School of Public Health, my parents, Maureen and Nehman, and my brother and sister, Lauren and Joseph for their ongoing encouragement, without which this dissertation would not have been possible.

1.0 IMPACTS OF VACCINE COLD CHAIN LOGISTICS ON THE EPIDEMIOLOGY OF VACCINATION IN NIGER AND THAILAND

1.1 LITERATURE REVIEW

1.1.1 Overview of vaccine supply chains

By 2019, twelve or more additional vaccines will be introduced to the immunization profiles of low and middle income countries (LMICs) to protect against diseases such as typhoid, dengue, malaria and shigella which already include several essential traditional vaccines (i.e., vaccines against tuberculosis, polio, measles, etc.)[1]. Global vaccine development has expanded in the last decade, providing countries with new and more effective vaccines and technologies to combat the spread of infectious diseases. While these advancements have enormous potential, their protective benefits can only be realized if there are effective ways of delivering vaccines to the people who need them.

Vaccine supply chains are the complex series of steps required to get vaccines from their domestic or international manufacturers through storage facilities at various levels in a country all the way to the health center level where vaccines can be administered to arriving patients[1]. The coordination of personnel, cold chain equipment, vehicle fleets, information systems, and activities seamlessly integrated with vaccine program and financial planning, forecasting, and production and procurement processes is essential. Without proper management and planning of

these activities, vaccines could not be delivered to the people who need them at the right time, place and in the right condition, increasing their risks for life-threatening diseases[1]. Vaccine supply chain logistics are becoming increasingly important, especially in LMIC's, or at countries' peripheries where public health infrastructure, access to reliable energy sources, and means of communication are weakest[1].

Furthermore, existing vaccine supply chains in many LMICs are already strained and face challenges in delivering the current vaccines of their Expanded Programs on Immunization (EPIs). Many countries' existing vaccine supply chains were conceptualized and designed in the mid 1970's when the World Health Organization (WHO) launched the EPI, and no longer meet the growing needs of the populations served or have the flexibility to accommodate future changes in the vaccines and accessories distributed[2]. With the total cost and volume of vaccines delivered per fully immunized child (FIC) expected to increase hundreds of times in the next decade, many countries' vaccine supply chains will face significant challenges in reliably delivering vaccines[2].

1.1.2 Vaccines in the Expanded Program on Immunization

Under the philosophy that preventing disease incidence through routine vaccination is more effective than treating illness, the EPI was launched in 1974 by the WHO to guide the distribution of vaccines, management of immunization systems and policies, regularly update and improve access to vaccine technologies. A primary long-term objective of the EPI was to accelerate disease control efforts and outcomes[3]. EPIs are typically governed by Ministries of Health (MOHs) in cooperation with the WHO and the United National Children's Fund (UNICEF), which provide technical assistance in planning, social mobilization, and resource

mobilization[3]. EPIs in each country distribute routine childhood vaccines recommended in all regions (e.g., vaccines against polio, tuberculosis and measles) as well as region-specific vaccines (e.g., vaccines against yellow fever and Japanese encephalitis) to reach vaccine-specific target immunization coverage rates and reduce the incidence and prevalence of VPDs[3]. The WHO has set forth recommendations on immunization schedules intended for use by national health policy-makers, immunization managers and other key decision-makers to ensure that the proper vaccines are administered to each age-specific target group[4]. However, in order for vaccine programs to be effective, they must reach their target population at the right time, the right place and the right condition before patients are exposed to infectious diseases.

1.1.3 Why model vaccine supply chains?

Changes may be made to vaccine regimens, vaccine product presentations, operating policies and storage and transport resources without considering their impacts on existing vaccine supply chain resources and their ability to impact vaccine coverage rates. Vaccine supply chains are used to distribute several products including vaccines, diluents, and injection accessories through hundreds of locations across a country, and each can have a range of transportation, inventory and administration policies. With so many disparate components to coordinate, planning supply chain operations can be complicated. Moreover, optimizing only one component of a supply chain at a time may have unanticipated adverse effects in other parts.

To manage these complexities, models can be used to formulate holistic, comprehensive representations of vaccine supply chains; identify the effects of decisions not immediately apparent; and highlight the importance of evaluating the potential complex, system-wide, dynamic effects of new supply chain strategies and interventions. For example, decisions made

earlier in the vaccine development and distribution process regarding vaccine presentations (e.g., vial size, mode of administration, temperature profile, and external packaging) and shipping procedures (e.g., lot sizes, palletized versus insulated shipping boxes, air versus freight transport methods, and delivery frequencies) can significantly impact whether vaccination clinics end up being oversupplied or undersupplied. To avoid these outcomes, models can help MOH's, vaccine managers and logisticians to:

(1) more accurately forecast vaccine needs based on patient demand which varies seasonally and geographically, and available vaccines and their vial size formulations,

(2) highlight supply chain locations needing additional storage, transport and human resources to accommodate current EPI schedules, new vaccine introductions, and increases in population demand,

(3) determine optimal between-level ordering, procurement, and distribution frequencies and policies, such as more frequent deliveries following a new vaccine introduction),

(4) identify and reallocate redundant resources such as unnecessary supply chain levels, cold chain devices, and personnel, and

(5) perform cost-effectiveness analyses of different interventions such as supply chain streamlining, vaccine introductions, vaccination campaign and outreach strategies, changing shipping network routing policies, or increasing vaccine storage length versus transport frequency.

Mathematically analyzing interventions to the vaccine supply chain can provide quantitative evidence for or against a certain strategy. For example, introducing a new vaccine results in storage bottlenecks that prevent the flow of vaccines to a number of locations. Consequently, such a vaccine introduction should be accompanied by a corresponding increase

in storage capacity at resource-limited locations. Evidence-based information provided by such analyses not only help national public health decision-makers better manage their supply chains and inventory, but can also be used to inform a wider host of stakeholders including: pharmaceutical manufacturers on vaccine target product profiles (TPP's); vaccine policy makers, financiers, and intermediaries such as the Global Alliance for Vaccines Initiative (GAVI), the World Bank, the Bill and Melinda Gates Foundation, and UNICEF; and international donor organizations such as the Japanese International Cooperation Agency (JICA) who provide annual cold chain equipment and vehicle donations to eligible countries for minimizing costly inefficiencies and improving health outcomes.

An example of where vaccine supply chain modeling would have been useful was prior to the introduction of two new rotavirus vaccines into several Latin and South American countries in 2006-2007. Due to the vaccines' relatively large volume, the rotavirus vaccines displaced other EPI vaccines from already limited space in the supply chains, compromising their abilities to distribute not only the rotavirus vaccines, but other essential routine vaccines as well. This lack of foresight resulted in unnecessary wasted doses, and in some locations, health workers, many of whom travel by foot, had to carry double the number of thermoses in order to transport the required vaccines. The sequelae from these introductions prompted vaccine manufacturers to formulate smaller presentations of the rotavirus vaccine[5, 6].

Different complexities exist in other countries. Kenya, for instance, has a complex web of parallel logistics systems catering to multiple health programs wherein twelve health commodities, which are procured by eighteen donor organizations, are supplied to sub-district health service providers through seven uncoordinated supply chains originating at five separate warehouses[1, 7, 8]. A study of four primary vertical programs in Kenya providing products for

family planning, tuberculosis, leprosy, vaccines, vitamin A, and essential drugs found that the four supply chains varied in coverage, availability and logistics system performance citing frequent chronic stock-outs, high vaccine wastage rates, poor inventory management, non-operational information systems, and a lack of transportation and communication between levels[7, 8]. Modeling these parallel supply chains could help currently ongoing reforms in the Kenyan health sector to improve systems efficiency by determining more optimal distribution strategies.

Several other projects are currently underway by various international stakeholders, initiatives and collaborations. Their collective aims are to improve the efficiency of immunization and health commodity systems by optimizing supply chain design and function. Some efforts to integrate parallel logistics systems are ongoing in Mozambique, Nepal, Tunisia, Togo, India, Ghana, Kenya, Malawi, Tanzania, Zambia and Zimbabwe. Efforts to outsource supply chain activities are being considered and applied in the United States, Botswana, Thailand, Ghana, Kenya, and South Africa, and streamlining is being implemented in Zimbabwe, Thailand and Indonesia[1, 8-15]. These studies are time consuming and expensive, and would require the temporary experimental mobilization of resources, including personnel and cold chain equipment, which may result in unanticipated declines in supply chain performance and vaccine coverage. Developing computational models to evaluate these interventions could save much time, money and effort; help inform decisions on future strategies; and result in significant public health benefits.

Computational modeling and operations research has long been used in disciplines such as finance, meteorology, transportation and aerospace, but its use to date in public health and LMIC's has been relatively limited[1, 16]. Three ways modeling can prove useful for vaccine

supply chain logistics include: (1) evaluating existing supply chain resources and improving current EPI outcomes, (2) assessing new supply chain strategies and interventions in specific regions or populations, and (3) advocating for policy change regarding evaluated vaccine supply chain entities[16]. Computational modeling of vaccine supply chains can help address some of the numerous and limiting challenges to vaccine delivery in resource-poor settings.

1.1.4 Existing and future challenges to sustainable vaccine supply chains

Most national vaccine supply chains have four to seven levels (i.e., airport store, national store, regional stores, provincial stores, district stores, sub-district stores, and commune health centers)[1]. Each level and shipment carries a risk of supply chain breakdowns and bottlenecks, which can jeopardize the condition of vaccines. Several existing key and future challenges to vaccine supply chains have been documented in the published and unpublished literature. such as expert opinion blogs and presentations.

Vaccine: New vaccines could be up to one-hundred times more costly and have larger volumes per dose than traditional vaccines[1, 2, 17]. As traditional vaccines have been supplied in multi-dose (i.e., 10 and 20-dose) vials, this has result ed in higher vaccine wastage. Partly due to their high cost, and to minimize vaccine wastage, new vaccines are packaged in 1 and 2-dose vials characterized by a higher volume per dose. Moreover, some of these vaccines are now being integrated or bundled with diluents (i.e., for freeze-dried vaccine formulations requiring reconstitution before injection), droppers, sprays or syringes to ensure maximum dose-delivery, and can therefore require over five-hundred times more physical space in the supply chain than traditional vaccines[1, 2].

Cold chain storage and transportation: Proper storage in warehouses and transportation is essential to maintaining a vaccine's immunogenic properties and ability to protect patients against disease[18]. Current and new vaccines will likely overwhelm already strained existing resources of national supply chains in LMICs (i.e., cold storage equipment, transportation devices and vehicles). Additionally the ability of supply chain managers to plan and forecast supply chain needs or develop transportation routes and schedules is often limited. Their selection of regional or climate-appropriate devices may not always be appropriate. The WHO's Performance, Quality and Safety recommendations for prequalified equipment standards are sometimes overlooked in favor of price of purchase[19, 20]. The difficulties of these tasks are compounded when vehicles, equipment or buildings must be shared between uncoordinated health programs and agencies where time and space must be allocated proportionally to accommodate each program's needs[1, 2]. The availability and employment of maintenance services for cold chain equipment is also often limited in LMICs. As a result of infrequent maintenance, these devices (e.g., cold trucks, refrigerators, freezers, etc.) are used for longer than their recommended lifetime, jeopardizing their ability to maintain ideal conditions for storing sensitive vaccines[19]. Furthermore, depending on where in the supply chain they occur, truck and equipment breakdowns, can lead to wastage of large batches of vaccines.

Access: Reliable electric power, a fundamental component of many medical services, is often limited in rural parts of LMICs[1, 18, 21]. Roughly 40% (350-400 million households) of the population in developing countries have no access to electricity[21]. Electric power grids are a primary source of energy and serve varying proportions of populations ranging from 98% in Thailand to 2-5% in parts of Sub-Saharan Africa[21]. In the absence of reliable power, vaccines cannot be stored for prolonged periods of time without experiencing adverse exposures to

excessive temperatures, which puts them at risk for spoilage. Studies conducted in Latin America, Southeast Asia, Africa, and Europe have demonstrated failures in maintaining proper temperatures for vaccine storage and transport[22]. Through immunoassays, other studies prove that exposed vaccines have resulted in sub-optimal potency[23, 24]. Solar powered technologies for buildings, equipment and vehicles are promising alternatives, but often prohibitively expensive, particularly for initial capital investments[25].

In addition to variations in the availability of reliable electricity, access may still be limited due to lack of infrastructure development in rural areas. Low road density, lack of paved roads and poor conditions of existing roads, particularly during monsoon seasons, make delivering vaccines challenging. Not only is there failure in delivering vaccines to health centers for vaccine administration, but patients may also fail to reach health centers in adverse environmental conditions. Additionally, political disturbances in some regions prohibit travel and therefore may limit vaccine availability to certain sub-populations[1, 26].

Target population: In additional to physical access to health centers, a number of other factors influence attendance at immunization sessions, including poor knowledge of immunization schedules, long wait times, poorly motivated service providers, inconvenient timing of immunization sessions, availability of transport, service charges, lack of prior notice to the community, cultural aversions to certain health services and fear of adverse events following immunization[27-31]. These dissuasions result in many children having incomplete vaccination series and remaining at risk for vaccine preventable diseases (VPDs)[27-31]. As a result, it is often difficult to know how many patients will arrive at each vaccination session. Given the variability in the number of patients arriving at each immunization session, inaccurate vaccine ordering can result in substantial open vial waste[32]. Information systems can possibly enable

greater transfer of information between administering and warehousing levels of a vaccine supply chain and could reduce the inaccuracies in forecasting vaccine needs, thus reducing the number of wasted doses by selecting appropriate vial sizes and immunization session frequency[33].

1.1.5 Difficulties in estimating vaccine coverage

In order to address the challenges associated with new vaccines, cold chain storage and transport equipment, access, and projections of target populations, understanding and improving the supply and distribution of vaccines requires an understanding of the epidemiology of vaccination and disease transmission (i.e., where and when vaccines are needed), and vice versa. VPDs are responsible for a majority of childhood deaths under 5-years[34]. To reduce disability, morbidity, and mortality associated with infectious disease transmission, country immunization programs must administer potent vaccines to susceptible women and children before they are exposed to VPDs. The ability of vaccines to prevent transmission of VPDs can only be realized if potent vaccines are available when and where they are needed.

By definition, immunization coverage is the proportion of the total target population, typically children under five years, that has received the recommended doses of vaccines[35, 36]. Immunization coverage is an important metric used to evaluate the level of protection in a population, to assess the performance of an immunization system, and for which universal targets exist[35]. If measured regularly, immunization coverage can serve as a sensitive indicator of location-specific system improvements or deteriorations. This information can guide efforts to strengthen vaccine supply chains, target service delivery, and provide a basis for comparison across countries and time[35].

The WHO and UNICEF request that countries report their annual vaccination coverage estimates through the Joint Reporting Form on Vaccine Preventable Diseases[37]. Vaccination coverage can be assessed through national surveys or randomized/cluster surveys using demographic household health surveys (DHS) or health service delivery records[36]. Methods to survey vaccination coverage recommended by the WHO and most commonly used are: (1) the EPI Cluster Survey using WHO methodology (30 by 7 cluster), (2) the Lot Quality Assurance Sampling (LQAS) technique, (3) Seventy-five Household Survey, (4) Missed Opportunity Survey, (5) Large-scale population based surveys, and (6) Computerized Information Systems[36, 38, 39].

Biases exist in reporting vaccination coverage, and therefore, such data should be interpreted carefully. For example, the number of patients in the target population receiving vaccines may be underestimated due to incomplete reporting which include undocumented vaccinations not or incompletely reported by all administering locations, or losses to follow-up of patients seeking vaccination outside their catchment area. Underestimation of the target population may also occur from non-inclusion of vaccinating sources, such as vaccinations administered by non-governmental organization or private health providers[36, 37]. Upwards biases by healthcare workers may result from pressures to achieve high coverage rates, or due to over-inclusion of the target group, which can occur when patients seek vaccination from health clinics outside their catchment areas[36]. Similarly, the number of individuals in the target population may also be biased due to population migration, inaccurate census estimates and projections, or multiple diverging sources of population data[36].

Reasons for inaccuracies in reported coverage rates between DHS estimates and coverage rates reported in the WHO Joint Reporting Form on Vaccine Preventable Diseases include: (1)

lack of data on vaccines administered through the public versus private sector, (2) ambiguity in antigen-specific vaccinations administered (i.e., caregiver recall bias), (3) lack of information systems and poor, untimely, and incomplete updating of patient records, (4) changes in data collection methods from year to year, (5) contradictions from dual reporting systems, or (6) existence of financial or non-monetary incentives for health workers to intentionally over-report the number of fully immunized children (FIC), which can all result in under-counting or over-counting of vaccinated individuals[36, 37].

For example, vaccination coverage rates in developing countries are typically overstated, and the validity of methods used to estimate changes in coverage rates over time is questionable[36, 37]. Shengelia et al.'s study on the comparison of vaccination coverage rates reported between 1990 and 2000 with those determined by demographic and health surveys (DHS's) in 45 countries studied, revealed a range of 11% to 77% in validity of DTP3 coverage rates[37]. Furthermore, it was determined that DTP3 coverage rates were systematically high, being overestimated by at least 20% compared to DHS estimates in over half of the studied countries[37]. Differences in socioeconomic status and level of development of health infrastructure are contributors to the differences in coverage validity across countries[37].

Computerized information systems are now increasingly being implemented in middle and low-income countries to track the number of vaccines administered, compute coverage rates, determine vaccine stock on-hand, vaccine wastage and disease incidence and monitor existing resources in the vaccine supply chain. Computerized information systems do not, however, prevent the entry of inaccurate data or the misuse of output generated from arithmetic computations.

1.1.6 VPD incidence and burden in unvaccinated populations

Despite reported gains in coverage, however, a large portion of the populations in LMIC's remain only partially vaccinated or unvaccinated. The epidemiology of VPDs varies by country and depends partly on vaccine uptake. In addition to supply chain-related interruptions in vaccine distribution, other factors contributing to sub-optimal vaccination coverage and the burden of disease include: level of education, socio-economic status, geography, religion, seasonal patterns, nutritional status, crowding and travel to and from other areas with circulating VPDs. Genetic differences may also contribute to the incidence of VPDs in different populations[40].

The greatest burden of disease lies in low-income countries. While Sub-Saharan Africa accounts for 80% of deaths from Yellow Fever, 58% of deaths from Pertussis, 41% of deaths from Tetanus, and 59% of deaths from Measles, East Asia and the Pacific account for 62% of hepatitis B deaths worldwide[40]. In 2001, vaccination averted approximately 94% of Diphtheria deaths (96% of which were in LMICs), 78% of Pertussis deaths (99% of which were in LMICs), 69% of Tetanus deaths (99% of which were in LMICs), 98% of Poliomyelitis deaths (100% of which were in LMICs), 62% of Measles deaths (99% of which were in LMICs), and 52% of Yellow Fever deaths worldwide (100% of which were in LMICs)[40]. Similarly, the proportion of disability-adjusted life years (DALYs) are most heavily bore by LMICs with 100% of 164,000 DALYs attributable to Diphtheria, 100% of 8,342,000 DALYs attributable to Tetanus, 99% of 11,542,000 DALYs attributable to Pertussis, 95% of 145,000 DALYs attributable to Poliomyelitis, 100% of 23,129,000 DALYs attributable to Measles, and 98% of 5,607,000 DALYs attributable to Meningitis[40].

Seroprevalence studies have been conducted in numerous settings to assess the attributable risk of seroprevalence (the number of people in a population who test positive for a

disease based on serology tests) on disease incidence for many of the childhood VPDs[41] and the importance of vaccine coverage and strengthening of immunization systems. A review of studies between 1980 and 2011 was conducted in Pubmed using combinations of the following search terms: ‘Unvaccinated children’, ‘Vaccination status’, ‘Seroprevalence’, ‘Serological status’, ‘Outbreak’, ‘Africa’, and ‘Asia’. In the majority of studies, disease morbidity, mortality, or disability were associated with: (1) unvaccinated populations, (2) partially vaccinated populations, or (3) vaccinated populations in areas where vaccine effectiveness was proven to be sub-optimal.

For example, in the 2006 rubella outbreak among 11-20 year olds in Kangra-Chamba, Himachal Pradesh, India, 61 cases were identified. Of the 61 cases, 50 had been vaccinated against measles, but only 2 had been given the MMR vaccine for additional protection against rubella[42]. Similarly, in 2004-2005, an ongoing outbreak of rubella in Georgia, 5151 cases of rubella were reported, and approximately 88% of cases were among unvaccinated individuals[43]. In a 1999 outbreak of poliomyelitis, the largest ever reported in Africa, 1093 cases occurred among 2 months-to-22 year olds in Angola. Vaccination status was known for 590 cases, of which 23% were unvaccinated, and 54% had received fewer than 3 doses of OPV[44]. A case control study of an outbreak in Tanzania in 2006-2007 reported 178 laboratory-confirmed measles cases, of which 46% had not received any measles vaccination, 37% had received one dose of the measles vaccine, and 17% had received both recommended doses[45]. Ensuing epidemics can have significant impacts on families in middle and low-income countries, where being ill means having to isolate oneself from family, miss work days, and purchase food and medicine with limited resources[46]. Moreover, epidemics have long-lasting impacts on

healthcare systems in resource-poor settings, where routine services cease, and essential vaccination clinics and campaigns get delayed or postponed[47].

Alternatively, the recent introduction of the new meningococcal A vaccine, "MenAfriVac™", in previously unvaccinated populations in Mali, Burkina Faso, and Niger in 2010 through immunization campaigns targeting 1-29 year olds is estimated to prevent over one million cases of meningitis over the next ten years[46]. Prior to this introduction, during one of the largest meningitis outbreaks in the meningitis belt (including countries such as Burkina Faso, Mali, Niger, Chad, northern Nigeria, Sudan and Ethiopia), over 250,000 cases were reported, among whom 25,000 deaths occurred[48]. In the next decade, use of the MenAfriVac™ in countries of the meningitis belt (total population: 240 million) was estimated to prevent approximately 142,000 deaths and 284,000 cases resulting in permanent disabilities, and is projected to save approximately $US656.8 million over the period costs associated with health care, laboratory, vaccine purchase and vaccine administration, freeing up resources that could be committed to other health initiatives[46].

A review of 102 studies of immunization program financing in 27 countries between 1979 and 2003 was undertaken to determine program costs of fully immunizing a child. The population-weighted cost of fully immunizing a child against the six traditional EPI antigens is approximately $US17.0 (range: $US3.0-$US31.0)[40]. The variation in costs was largely due to differences in the overall scale of the program, differences in vaccine selection and prices, differences in distribution and warehousing strategies and differences in personnel salaries and per diems across countries[40]. The cost per FIC by World Bank designated region was $US13.25 (cost per death averted: $US434.00), $US14.21 (cost per death averted: $US205.00), $US17.11 (cost per death averted: $US205.00), $US18.10 (cost per death averted: $US1,030.00),

$US24.12 (cost per death averted: $US3,540.00), and $US22.15 (cost per death averted: $US993.00) for East Asia and the Pacific, Sub-Saharan Africa, South Asia, Latin America and the Caribbean, Europe and Central Asia, and the Middle East and North Africa[40]. Considering the potential costs of death or treating disabilities associated with VPDs, vaccination is a highly cost-effective means of reducing morbidity and mortality worldwide.

1.1.7 Overview of Thailand and Niger demographics, vaccination coverage and EPIs

In 2010, Niger had a total population of 15,891,000 people (3,421,000 less than five years, 7,966,000 less than 15 years, and 3,424,000 females 15-49 years), 838,000 live births, and 768,000 surviving infants[49]. Niger is a landlocked country (1,266,700.0 square kilometers), with a development status classified by the WHO as 'least developed', with a gross domestic product (GDP) per capita of $US660.0, a thirty-two percent primary education completion rate, an infant (less than 12 months) mortality rate of 79 per 1,000 infants, and a child (under 5 years) mortality rate of 167 per 1,000 children[49]. Life expectancy at birth is 52 years (2009), adult literacy rate is 29% (2005), and the poverty headcount ratio at the national poverty line is 59.5% of the total population (2007)[50]. Eight-three percent of the population is rural, and 21% of all roads in the country are paved[50].

The Niger EPI includes six vaccines: Bacille Calmette-Guerin (BCG) against Tuberculosis administered at birth, pentavalent Diphtheria-Tetanus-Pertussis-Hepatitis B-Hemophilus Influenzae type B (DTP-HepB-Hib) administered at 6, 10 and 14 weeks of age, measles (M) administered at 9 months, oral polio vaccine (OPV) administered at birth, 6, 10 and 14 weeks of age, Tetanus Toxoid (TT) administered during pregnancy and to women of childbearing age, and Yellow Fever (YF) administered at 9 months[49]. Niger's vaccine supply

chain has one central store, eight regional stores, forty-two district stores and six-hundred-ninety-five integrated health centers. In 2010, sixty-four percent of districts report greater or equal to 90% DTP3 coverage, twenty-six percent report 80-89% DTP3 coverage, and ten percent report 50-79% DTP3 coverage[49]. Niger has yet to introduce the second dose measles vaccine, mumps, pneumococcal, rotavirus or rubella vaccines into the routine EPI schedule[49]. The country has a comprehensive multi-year plan for immunization (cMYP) forecasting vaccination needs and targets until 2015. Additionally, all districts have microplans for improving vaccination coverage[49].

By contrast, in 2010, Thailand had a total population of 68,139,000 people (4,850,000 children less than five years, 14,629,000 people under 15 years, and 18,897,000 women 15-49 years), 976,000 live births, and 969,000 surviving infants[51]. Thailand, situated in the middle of Southeast Asia, borders both the South China and Andaman seas with an area of 514,000 square kilometers and is flanked by Laos, Burma and Cambodia[51]. Its development status is classified by the WHO as 'developing', with a GDP per capita of $US7,640.0, infant mortality rate of 13 per 1,000 infants, and child mortality rate of 14 per 1,000 children[51]. Life expectancy at birth is 69 years (2009), the adult literacy rate is 94% (2005), and the poverty headcount ratio at the national poverty line is 8.1%. Sixty-six percent of the total population is rural[52].

Thailand's EPI contains seven routine vaccines including: BCG and HepB administered at birth, DTP-HepB administered at 2, 4, and 6 months, Japanese Encephalitis (JE) administered at 1.5 and 2.5 years, Measles-Mumps-Rubella (MMR) administered at 9 months and in school-aged children, OPV administered at 2, 4, 6, and 18 months and 4-5 years, and TT administered during pregnancy[51]. In 2010, the WHO-UNICEF coverage estimate for DTP3 was 99% across

the entire country, and like Niger, Thailand has a cMYP for forecasting vaccine needs and targets until 2012[51].

1.1.8 Existing vaccine supply chain models

Vaccine supply chain models exist in multiple forms ranging in complexity from spreadsheet models to complex stochastic simulation models. These models are widely used to evaluate the performance of vaccine supply chains by combining information on available cold and dry storage space, transportation fleets, target populations, vaccine characteristics and schedules, shipment routing networks, cost of supplies, equipment, and personnel resources to generate various supply chain performance metrics and inform optimal supply chain design.

There are currently several modeling tools available to help public health decision makers understand the impacts of various supply chain interventions for the distribution of health commodities and the evaluation of health strategies. . Some of these models are available in the public domain. The following are four health commodity supply chain models in development:

(1) The Unified Health Model (UHM): Partners from UN agencies (WHO, UNICEF, WB, UNFPA, UNDP, and PMNCG) and the Futures Institute have developed the UHM, a publically available joint UN health sector strengthening tool for costing and evaluation of national strategies, action plans or interventions and preparedness plans with individual modules for EPI strategies for logistics and specific communicable diseases, nutrition, sanitation, and water in an effort to assist countries in reaching the MDGs. The objective of the model is to forecast the demands on a system, bottlenecks, resource mobilization, and financial sustainability of health system interventions at national and regional levels[53].

The supply chain logistics module of the UHM for health commodities is developed by LLamasoft[54]. Currently, this model only has a complete set of data for the continent of Africa and it extends as far as the district level. Inputs to the logistics module will include: material requirements, product information (e.g., packaging dimensions of health commodities), and contextual country or system characteristics (e.g., geo-coded population data, facility information, etc.). Outputs include supply chain network structures, and logistics, financial, and network service performance metrics[53].

(2) The 2020 Supply Chain Model: The USAID Deliver Project, in collaboration with other partners, had developed the 2020 Supply Chain Model to assess a country's national morbidity patterns and determine the necessary material and health commodity requirements to meet treatment and prevention targets in the years 2020 to 2025. The 2020 Supply Chain Model uses the Supply Chain Guru software package. Not only does the model focus on the prevention and treatment of specific diseases, but also the material requirements for family planning services. This model is a planning tool to ensure that public health policy makers are equipped with information on evolving needs of their supply chains in the coming ten years[53].

(3) Optimize Supply Chain Model: Project Optimize, a collaboration between the WHO and PATH, developed an economic supply chain model using Microsoft Excel and ARENA logistics simulation software. The model is designed to help public health decision makers in different country settings understand and evaluate the benefits and costs of changes to their vaccine and health commodities supply chains by providing visualizations of transport and cold chain equipment, and warehouse components[53].

(4) The Highly Extensible Resource for Modeling Event-driven Simulations (HERMES): The Vaccine Modeling Initiative (VMI) is a Bill and Melinda Gates funded project

to develop models for better understanding vaccine development, distribution, and delivery. The VMI has developed HERMES, a custom-designed supply chain logistics stochastic simulation model. HERMES is built upon SimPy, a discrete event simulation engine, and written in the Python programming language. HERMES can be rapidly applied to any country and supply chain context, and has the ability to represent every vaccine, health commodity, storage device, transport vehicle or device, network structure, and many operating policies.

Simulations in HERMES represent the flow of vaccines through each of these structures. Inputs to HERMES include: product presentation information (e.g., packaging dimensions of vaccines and diluents), and contextual country or system characteristics (e.g., geo-coded population data, facility information and their functions, routing networks, etc.), which can be incorporated in as much detail as required to address a given query. Outputs can be provided in multiple forms including, but not limited to: storage capacity utilization, transport capacity utilization and overfill, vaccine availabilities, stock inventory histories, and frequency and magnitude of stock-outs. A unique feature in HERMES is a temperature monitoring function on each vaccine in the supply chain to determine the number wasted vials from temperature excursions outside their recommended profiles[53, 55].

1.1.9 Addressing a gap in the literature

To date, models of vaccine supply chain logistics have been relatively under-utilized in informing public health decision-making. The three research studies comprising this dissertation aim to fill gaps in the literature and will highlight the importance of considering existing supply chain resources when planning or changing routine vaccination programs. Each study aims to evaluate the impact of a different form of modification to a vaccine supply chain by making

changes to the: (1) immunization program, (2) supply chain network, and (3) vaccine administration policies. Together, the studies will illustrate how computational modeling of vaccine supply chains can illustrate how operational, programmatic and structural changes to a country's vaccine supply chain can impact vaccine coverage and ultimately, infectious disease epidemiology.

2.0 IMPACT OF CHANGING THE MEASLES VACCINE VIAL SIZE ON NIGER'S VACCINE SUPPLY CHAIN: A COMPUTATIONAL MODEL

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This manuscript has been published in the BMC Public Health Journal

Assi TM, Brown ST, Djibo A, et al. Impact of changing the measles vaccine vial size on Niger's vaccine supply chain: a computational model. *BMC Public Health* 2011;11:425.

2.1 ABSTRACT

2.1.1 Background

Many countries, such as Niger, are considering changing their vaccine vial size presentation and may want to evaluate the subsequent impact on their supply chains, the series of steps required to get vaccines from their manufacturers to patients. The measles vaccine is particularly important in Niger, a country prone to measles outbreaks.

2.1.2 Methods

We developed a detailed discrete event simulation model of the vaccine supply chain representing every vaccine, storage location, refrigerator, freezer, and transport device (e.g., cold trucks, 4x4 trucks, and vaccine carriers) in the Niger Expanded Program on Immunization (EPI). Experiments simulated the impact of replacing the 10-dose measles vial size with 5-dose, 2-dose and 1-dose vial sizes.

2.1.3 Results

Switching from the 10-dose to the 5-dose, 2-dose and 1-dose vial sizes decreased the average availability of EPI vaccines for arriving patients from 90% to 87%, 86% and 80%, respectively for a 100% target population size. The switches also changed transport vehicles utilization from a mean of 58% (range: 4-164%) to means of 59% (range: 4-164%), 62% (range: 4-175%), and 67% (range: 5-192%), respectively, between the regional and district stores, and from a mean of

160% (range: 83-300%) to means of 161% (range: 82-322%), 175% (range: 78-344%), and 198% (range: 88-402%), respectively, between the district to integrated health centers (IHC). The switch also changed district level storage utilization from a mean of 65% to means of 64%, 66% and 68% (range for all scenarios: 3-100%). Finally, accounting for vaccine administration, wastage, and disposal, replacing the 10-dose vial with the 5 or 1-dose vials would increase the cost per immunized patient from $0.47US to $0.71US and $1.26US, respectively.

2.1.4 Conclusions

The switch from the 10-dose measles vaccines to smaller vial sizes could overwhelm the capacities of many storage facilities and transport vehicles as well as increase the cost per vaccinated child.

2.2 INTRODUCTION

Many countries, such as Niger, are considering changing their vaccine vial size presentations, i.e. number of doses per vial. Single dose vials reduce contamination risk, inaccurate dosing, and vaccine wastage, but increase space requirements, medical waste volume and costs per dose[5, 32, 56, 57]. Countries changing vaccine vial size presentations in their World Health Organization (WHO) Expanded Programs on Immunization (EPI) should evaluate the subsequent impact on their supply chains, the series of steps required to get vaccines from their manufacturers to patients. The measles vaccine is particularly important in Niger, a country prone to measles outbreaks[58, 59]. In 2003, health officials in Niger reported 50,138 cases and 201 deaths from measles[58]. Providing to children, especially in rural areas, has been challenging[58, 59].

The Vaccine Modeling Initiative (VMI), funded by the Bill and Melinda Gates Foundation, collaborated with the Ministry of Health and WHO in Niger and other partners, to develop a computational model of the national vaccine supply chain. We developed a model of the Niger vaccine supply chain representing the flow of all WHO EPI vaccines from manufacturers, to the central storage facility (Niamey), through each subsequent level of the supply chain, and finally to vaccine recipients at integrated health centres (IHCs) (i.e., service delivery level). Using this model, we simulated the replacement of multi-dose measles vaccines with vaccines in smaller vial sizes to determine the impacts on the supply chain.

2.3 METHODS

2.3.1 General Framework

The Highly Extensible Resource for Modeling Supply Chains (HERMES), a custom-designed, dynamic, discrete event simulation model (DES), is written in the Python programming language, using features provided by the SimPy package[60]. This model explicitly simulates all processes, storage locations, administering locations, and storage equipment in the Niger vaccine supply chain.

2.3.2 Niger Vaccine Supply Chain and Data Sources

Figure 1 shows the four levels of the supply chain. Data to construct the models was collected from the WHO in Geneva, WHO in Niger, UNICEF, the Niger National Geographic Institute (NGI), the Niger Ministry of Health (MOH), the WHO EPI in Niger, and direct field observations. In 2009, the following data was collected in-country to begin model development: cold chain equipment inventory[61], transportation resources; operating polices for shipments, storage, and aspects of vaccine administration; and patterns of patient arrival.

The number of vaccines administered at the IHCs is a function of the population demand. The population demand is estimated using district-level birth registry data from 2005 (557,381 total newborns across all districts) adjusted by an annual growth rate of 1.04% to 2010 (586,880 total newborns across all districts) to account for population growth[62]. Newborns are distributed among the 695 IHC sites, and each of the immunization sessions each month. Each

time a patient arrives for vaccination at an IHC, he or she receives the appropriate age-specified (0-11 month, and 12-24 month old children) vaccines, if they are available.

2.3.3 Model Structure

We chose to utilize a DES model because the effects of changing the measles vaccine vial size may be subtle, complex, dynamic and not captured by less detailed representations. For example, changing vial size can affect the ability of a clinic to fulfill demand and the amount of open vial wastage, which affects a clinic's order sizes, effects that may propagate up the supply chain.

In HERMES, each vaccine vial is an entity complete with its own set of relevant characteristics such as vaccine antigen type, doses per vial, shelf-life, formulation, and package volume. Each Niger EPI vaccine vial [i.e., Bacille Calmette-Guérin tuberculosis (BCG), oral polio (OPV), measles, yellow fever (YF), tetanus toxoid (TT), and the diphtheria-tetanus-pertussis-hemophilus influenzae type B-hepatitis B (DTP-HepB-Hib) vaccines] is represented as an entity. Each vaccine vial entity begins at the manufacturer and is packaged into a shipping lot with other vial entities. From there, the entity gets delivered with the shipping lot to the central store where the entity is unloaded, repackaged into a smaller lot and stored in cold room until it is scheduled for further shipment. When shipment time comes, depending on its destination, it will either be loaded into cold trucks destined for regional stores, or 4x4 trucks destined for district stores, where it will be unloaded, repackaged into a smaller lot and stored in a cold room, refrigerator or freezer. A district store will use its 4x4 truck to collect the entity in its lot whenever its inventory is depleted by downstream clinics. A clinic will then send its vaccine carrier to its district store to collect the entity in its lot when the clinic reaches its re-order point.

At each storage location and transport vehicle, an entity has a probability of breakage from mishandling. The entity also has a specified lifetime beyond which its doses expire.

Based on WHO recommendations, HERMES assumes that clinics and district stores re-order points are 25% of their maximum and that orders will account for a 25% buffer[63]. When cold space is limited, HERMES uses a balanced allocation scheme wherein complete vaccine regimens (i.e., all doses required for full immunization) are prioritized over single antigens, and a 'first-in-first-out' policy is used every time a vaccine is removed from a storage or transport device. Each simulation represents a one-year time horizon over which statistics on vaccination rates, stock-outs, vial expiration, and storage and transport utilization are accumulated.

Each refrigerator maintains a temperature of 2°C to 8°C and each freezer a temperature of -15°C to -25°C. Each vaccine's required temperature profile determines whether it will be stored in freezer or refrigerator compartments.

Current vaccine inventory in each cold room, freezer, refrigerator, or transport device (i.e., the number of vaccines currently stored in that device) is equal to the number of vaccines arriving that day plus the number of vaccines left over from the previous day minus the number of vaccines removed (to either be shipped or administered).The model does not allow the total vaccine inventory stored in a refrigerator, freezer, or cold room to ever exceed the device's storage capacity.

Open vial wastage occurs when vials are opened by not all the doses are completely consumed before expiration (e.g., only two doses used from a five-dose vial) as detailed by a previously published study and the WHO's Multi-Dose Vial policy (MDVP)[5, 64].

2.3.4 Vaccine Specifications

Table 1 lists Niger's six EPI vaccines[65], [66, 67]. Information from previous studies was used to compute the cost of contaminated medical waste disposal[68]. The volumes of the diluents are considered, but only consume space at the IHC locations several hours prior to vaccine administration.

Niger currently supplies measles vaccines in 10-dose vials (2.61cm^3 per dose). Our analysis explores the effects of substituting the measles vaccine dose administered at age <1 year from the 10-dose vial with a 5, 2 or 1-dose vaccine presentation.

2.3.5 Supply Chain Performance Metrics

Vaccine availability (equation 1) is computed for each simulation for each vaccine type at each IHC:

$$[1]\ Vaccine\ Availability = \frac{Number\ of\ patients\ receiving\ vaccine\ per\ year}{Number\ of\ patients\ arriving\ at\ an\ IHC\ per\ year}$$

The transport capacity utilization rate (equation 2) for each transport device (e.g., truck, cold box or vaccine carrier) and the storage utilization rate (equation 3) for each refrigerator and freezer are computed for each simulation run:

$$[2]\ Transport\ Capacity\ Utilization = \frac{Transport\ space\ consumed\ in\ vehicle\ per\ shipment}{Total\ transport\ space\ available\ in\ vehicle\ per\ shipment}$$

[3] $Storage\ Capacity\ Utilization$

$$= \frac{Storage\ space\ consumed\ in\ cold\ chain\ equipment\ per\ storage\ period}{Total\ transport\ space\ available\ in\ cold\ chain\ equipment\ per\ storage\ period}$$

Using input values from Tables 1 and 2, equations 4-8 are employed to calculate costs of using a single versus multi-dose vial (i.e., cost of vaccine dose administration, wastage, and disposal)[69] . A generally accepted discounted rate of 3% updated costs to 2011 United States dollars ($US)[70]:

[4] $Cost\ of\ Using\ Single-dose\ Vial$

$$= Cost\ of\ administering\ a\ dose + Cost\ of\ disposal$$

[5] $Cost\ of\ Using\ Multi-dose\ Vial$

$$= Cost\ of\ administering\ a\ dose + Cost\ of\ wasted\ doses$$
$$+ Cost\ of\ disposal$$

[6] $Cost\ of\ Vaccine\ Administration$

$$= (Cost\ of\ vaccine\ per\ dose \times Number\ of\ doses\ administered)$$
$$+ (Cost\ of\ administration\ syringe \times Number\ of\ doses\ administered)$$
$$+ Cost\ of\ total\ number\ of\ reconstitution\ syringes$$

[7] $Cost\ of\ Wasted\ Doses = Cost\ of\ vaccine\ per\ dose \times Number\ of\ wasted\ doses$

[8] $Cost\ of\ Disposal$

$$= Safety\ box\ cost\ per\ dose + (Waste\ disposal\ cost\ per\ kg \times (Weight\ of\ a\ vial + weight\ of\ a\ reconstitution\ syringe + weight\ of\ total\ number\ of\ administration\ syringes))$$

The price per dose of the 2-dose measles vial size is unknown. The price per dose of the 5-dose vial is taken from a previous study which used linear regression analysis on all available vaccine vial sizes to estimate three price points[69]. All other vial size prices per dose are taken from the 2009 WHO Vaccine Volume Calculator[67].

Each vial size scenario is simulated and averaged over ten replications. Due to stochasticity, the number of arriving patients in each scenario varies slightly across vial size scenarios.

2.3.6 Sensitivity Analyses

Sensitivity analyses systematically ranged the following parameter: inventory loss rate (range: 0-2%), shipping loss rate (range: 0-2%), storage capacity utilization (85-100%), population demand (static [i.e., number of patients in a month is fixed based on projected population estimates and does not fluctuate from month to month] versus dynamic monthly distribution [i.e., number of vaccine recipients in a given month draws from a Poisson distribution with a mean of (λ)]), and percentage of the target population that actually arrives at IHCs to be vaccinated (60-100%).

Model validation consisted of running similar scenarios in a previously published deterministic equation-based model and observing convergence in results from both models[71]. We also compared the trends seen in our experiments with those from other similar field studies in other countries[72].

2.4 RESULTS

Sensitivity analyses demonstrated that varying the patient demand (static versus dynamic), shipping and inventory loss, and storage capacity utilization did not notably affect the pattern of results. Varying the target population that actually arrived at an IHC to be vaccinated had noteworthy effects on vaccine availability, transport and storage utilization. Therefore, the following results report from scenarios representing 1% inventory and shipping loss, 100% capacity utilization, and dynamic monthly demand for target population sizes of 100%, 80% and 60%.

2.4.1 Overall Impact

Our model results suggest that the larger packaged volumes per dose of the 1-dose, 2-dose, and 5-dose measles vial sizes reduce vaccine availability at IHC's. Smaller vial sizes create greater bottlenecks in the already constrained region-to-district and district-to-IHC transportation devices. Moreover, while larger vial sizes result in more wasted doses, their lower price per dose provides relative cost savings. Additionally, the increased number and volume of vials and

injection accessories (e.g., injection and reconstitution syringes) associated with smaller vial sizes results in substantial increases in waste disposal costs.

2.4.2 Impact on Vaccine Administration

Switching from the 10-dose to the 5-dose, 2-dose and 1-dose measles vaccine vial size decreased the percent of arriving patients receiving vaccines (vaccine availability) from 90%, (58,482 of 583,575 measles vaccination opportunities being missed), to 87% (75,116 of 583,477 missed vaccination opportunities), 86% (84,307 of 583,722 missed measles vaccination opportunities) and 80% (117,167 of 583,264 missed measles vaccination opportunities), respectively, across the entire country.

Table 3 lists vaccine availabilities for other EPI vaccines across 60%, 80% and 100% target population sizes. Not only do the smaller vial size scenarios affect availability of the measles vaccine, but the average availability across other current EPI vaccines also decreased slightly on following the switch.

2.4.3 Impact on Vaccine Transport

Figure 2 shows frequency histograms for transport capacity utilization between the region and district, and district and IHC levels across different vial size scenarios. In the first column, each bar in a histogram represents the number of transport vehicles along a route experiencing a certain percentage of capacity utilization. For example, in the first panel, for all vial size scenarios, 5 of the 7 central-to-region transport routes outside the two shipping loops are filled to 100% of their available capacity. In this figure, any transport capacity utilization exceeding

100% is the demand requested utilization from a downstream location, while the actual utilization of the vehicle is limited to 100%. For example, if an IHC needs 100 vials but their transport device can only carry 50, their transport device will be overfilled, its transport utilization will be 200%, but it can send at most 100% (or 50 of 100 vials). Those portions of the orders above 100% go un-served and are added to the next shipment.

There was enough cold transport capacity for vaccine shipments from the central store to the regional stores in the two shipping loops for all vial size scenarios only changing the median utilization from 66% for the two cold trucks which distribute vaccines to 7 regional stores, to 66%, 71% and 77% for the 5-dose, 2-dose and 1-dose vial sizes, respectively. However, the 7 district stores in the region that procure their own vaccines in 4x4 trucks consistently experienced overfill from an median across transport routes of 68% transport capacity utilization (range: 32-615%) for the 10-dose vial size scenario, to 74% (range: 32-616%), 80% (range: 32-659%) and 90% (range: 32-720%) for the 5-dose, 2-dose and 1-dose vial size scenario, respectively, resulting in many necessary vaccines in excess of available transport capacity not being delivered.

Similarly, the bottleneck in transport continues from regional to district level stores, wherein with the exception of one district store that has no cold storage capacity, the median 4x4 truck capacity utilization across transport routes changed from 53% (4-164%) in the 10-dose vial size scenario to 55% (range: 4-164%), 56% (range: 5-175%) and 56% (5-192%), respectively.

Bottlenecks in transport continue to have an impact from district to IHC's wherein the median vaccine carrier capacity utilization across transport routes changed from 149% (range: 83-300%) in the 10-dose vial size scenario to 154% (range: 82-322%), 168% (range: 78-344%) and 189% (range: 84-402%) for the 5-dose, 2-dose and 1-dose vial size scenarios, respectively. Reducing the target population to 80% and 60% reduces the median utilizations of cold trucks by

up to 20% from the previous scenario, 4x4 trucks (central to regional) by up to 18%, 4x4 trucks (region to district) by up to 10%, and vaccine carriers by up to 20%, respectively.

2.4.4 Impact on Vaccine Storage

Figure 3 shows frequency histograms of the storage capacity utilization at the regional, district, and IHC stores across vial size scenarios. While cold room capacity utilization at the central level did increase for some scenarios from 65% in the 10-dose vial size scenario to 65%, 70% and 76%, for the 5-dose, 2-dose and 1-dose vial size scenarios, respectively, there was ample room for future vaccine introductions or storage of other temperature sensitive products.

The regional level also had enough capacity to accommodate the added volume from the smaller vial sizes only changing the median capacity utilization for some scenarios across regional stores from 12% (range: 1-27%) in the 10-dose vial size scenarioto 15% (range: 1-27%), 16% (range: 1-29%), and 17% (range: 1-33%) in the 5-dose, 2-dose, and 1-dose vial size scenarios, respectively.

Storage capacity bottlenecks first emerged at the district level with median district level refrigerator utilization across district stores changing slightly for some scenarios from 63% in the 10-dose vial size scenario to 63% , 67% , and 73% (range for all scenarios: 3-100%). The number of district stores exceeding 80% of their available refrigerator capacity changed for some scenarios from 17 to 16, 17 and 18 stores out of 42, many of which exceeded even 95% of their available storage space for the 5-dose, 2-dose and 1-dose vial sizes, respectively.

Given the persistent district level storage and transport bottlenecks with decreasing vial size, fewer vaccines were able to reach the IHC level and the median storage capacity utilization across IHC's did not change substantially from 33% (range: 3-99%) for the 5-dose vial size, 34%

(range: 0-98%) for the 2-dose vial size, and 36% (range: 0-97%) for the 1-dose vial size compared to 34% (range: 4-98%) in the 10-dose vial size scenario. Moreover, the number of IHC stores exceeding 80% of their storage capacity decreased slightly in some scenarios from 67 to 61, 67 and 87 of 695 stores for the 5-dose, 2-dose and 1-dose vial sizes, respectively. Reducing the target population from 100% to 80% reduces the median storage capacity utilization across levels by 0-4% and from 80% to 60% by 5-20%.

2.4.5 Impact on Vaccine Supply Chain Costs

Despite reductions in open vial waste with the 5-dose, 2-dose and 1-dose vial sizes compared to the 10-dose vial size, the number of doses saved was outweighed by the costs associated with the increasing price per dose and cost of waste disposal as vial sizes decreased. The number of wasted doses of the measles vaccine decreased from 1,279,450 for the 10-dose vial size to 442,398, 96,357 and 0 for the 5-dose, 2-dose and 1-dose vial sizes, respectively. However, the total costs of wasted doses from open vial waste increased from $33,391US for the 10-dose vials ($0.25US/dose) to $42,205US (range: $38,046US-$46,894US) for the 5-dose vials ($0.48US/dose, range: $0.43US-$0.53US) per year across Niger on account of the increasing cost per dose with decreasing vial size. The cost of the 2-dose vial was unknown and the 1-dose vial size ($0.94US/dose) produced no open vial waste. Similarly, as the vial size decreased, the cost of vaccine administration more than doubled from $179,779US in the 10-dose vial size scenario to $287,131US (range: $263,194US-$314,124US) and more than tripled to $586,214US in the 5-dose and 1-dose vial sizes, respectively. Finally, the increased volume of vials and injection material per dose with smaller vial sizes resulted in increased costs of contaminated waste disposal from $31,588US to $33,275US and $55,025US. All three cost components combined

translate to a total cost increase from $244,759US to $362,611US ($334,515US-$403,279US) and $586,214US, or to an increase in the cost per injection from $0.47US in the 10-dose vial size scenario to $0.71US ($0.66US-$0.77US) and $1.26US in the 5-dose and 1-dose vial size scenarios.

Given that there were fewer administered doses with the 5 and 1-dose vial size scenarios, these costs would likely increase if there were enough storage and transport capacity to achieve baseline measles vaccine availabilities or higher.

2.5 DISCUSSION

Results suggest that while selecting smaller vial sizes substantially reduces open vial waste, current storage and transport resources at the district and IHC levels of the Niger vaccine supply chain are pushed to their capacity, which results in lower vaccine availability of smaller vial sizes at the IHC level. The increased space requirement associated with the smaller vial sizes could also limit the supply chain's flexibility to respond to sudden changes that would require extra capacity (e.g., vehicle breakdown, refrigerator failure, etc.) or future anticipated increases in vaccine throughput from the introduction of new and under-utilized vaccines. Moreover, decreasing the vial size would increase the cost of the vaccine per dose and the total volume of vials and safe injection equipment in the supply chain, thereby increasing the costs of vaccine administration and waste disposal, which far outweigh the costs saved from the decrease in wasted doses.

Several noteworthy effects resulted when we reduced the target population to 80% and 60% of total EPI-eligible children: 1) smaller session sizes were associated with higher vaccine wastage, and 2) the wastage rate varied across vaccine types (i.e., liquid versus lyophilized), and across vial sizes (i.e., 1, 5, 10 and 20 doses per vial). For example, OPV, DTP-HepB-Hib, and TT had lower wastage than measles, BCG and YF because according to the WHO's MDVP, these liquid vaccines can be kept up to 4 weeks after opening[64]. The smaller vial sizes experienced higher wastage than the larger vial sizes, particularly for smaller session sizes. These are important findings that have also been reported in other field program evaluations in similar settings, and suggest tailoring vial size selections to anticipated session sizes[72]. For example, 1 and 2-dose vials can be used efficiently for birth doses, whereas 10 and 20-dose vials would be better suited for mass vaccination campaigns or IHCs with larger volumes of patients. This may require customizing re-order policies for specific regions, districts, or IHCs where demand for vaccines is highly variable. Scaling up orders based on global estimates of vaccine-specific open vial waste for the whole supply chain, especially ones with high population variability may lead to over or under-ordering vaccines in some locations.

Our findings highlight the importance of considering the effects on existing supply chain resources when changing the presentations of vaccines in a country's EPI. Introducing a new vaccine presentation into a supply chain with limited resources can not only affect the supply of that vaccine, but also of all other vaccines in the EPI, which could ultimately hinder important infectious disease control efforts. Simulations of vaccine distribution through supply chains prior to any change in the EPI vaccines or to the structure of the supply chain itself can help pinpoint series of locations along the chain where bottlenecks, stock-outs, or overstocking may occur.

These evaluations can then inform public health decision makers and logisticians on where the addition of new resources (e.g., refrigerators, freezers, trucks, etc.) would be most beneficial.

Additionally, our findings also illustrate the importance of considering medical waste when introducing a new vaccine presentation or vaccine technology. Improperly disposing of waste can result in harmful exposure to blood borne pathogens. The costs of effective systems to safely remove contaminated medical waste and prevent infection often include costs for separating, sorting, treating, and transporting different kinds of waste products to disposal facilities where they can be either buried or incinerated[73].

However, rather than discourage the use of single-dose vaccine presentations, our findings simply help identify some of the programmatic and economic repercussions of switching from 10-dose to 5-dose, 2-dose or 1-dose vaccine presentations. Smaller vial size presentations offer certain benefits not accounted for by our study. The 1-dose presentation may allow for more consistent dose-size administration, reduce the risk of cross-contamination from repeated entry by reconstitution syringes and injection syringes for administrations, and provide more convenience to health care workers who would otherwise have to keep track of the number and volume of doses they withdraw. Eliminating open vial wastage may also alleviate the need for policies to plan when and when not to open new vials in response to arriving patients in order to minimize open vial wastage.

Our study illustrates how models can be applied in different scenarios to identify the effects of decisions not immediately apparent. Models have been commonly used for decision making in many other industries, such as manufacturing[74], meteorology[75], transportation[76], aerospace[77], finance[78], and sports and rehabilitation[79]. Conversely, their uses in public health have been relatively less extensive[80-82]. Of late, models in public

to the spread of infectious disease (e.g., the 2009 H1N1 influenza pandemic) and health-care associated infections[83-87], but much of their potential applications remain untapped.

2.5.1 Limitations

Given that models are by definition, simplified representations of real life, they cannot capture every potential factor, event, or outcome[88, 89]. Additionally, the data parameters included in our model are collected up to 2010 and may not represent future changes that may occur in the Niger vaccine supply chain. Due to the paucity of available data, the actual daily patient demand may vary from our estimated demand. Furthermore, developing our model involved substantial data collection including obtaining records from and conducting interviews at different locations in and out-of-country and came from a wide variety of sources. Thus, parameter values may vary in accuracy and reliability. Despite these limitations, sensitivity analyses demonstrated that model outcomes are robust under a wide variety of circumstances.

2.6 CONCLUSIONS

While smaller vial sizes of the measles vaccine lead to decreases in open vial waste, the capacity of several storage sites and transport routes in the Niger vaccine supply chain are insufficient to accommodate their higher volumes per dose, which result in lower vaccine availability for arriving patients. Moreover, at higher prices per dose, the costs of wasted doses and contaminated

waste disposal ultimately outweigh the benefits provided by reducing or eliminating open vial waste.

2.7 ACKNOWLEDGEMENTS

This study was supported by the Vaccine Modeling Initiative (VMI), funded by the Bill and Melinda Gates Foundation and the National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) grant 1U54GM088491-0109. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. We would also like to acknowledge the important contributions of the following individuals to our study: Dr. Amadou Garba (Schistosomiasis Control Initiative), Dr. Tiekoura Coulibaly (EPI Officer, WHO Niger), Dr. Abdou M. Chitou (EPI Administrator, UNICEF Niger), and Mr. Harou Moussa (EPI Office, WHO Niger).

2.8 FIGURES

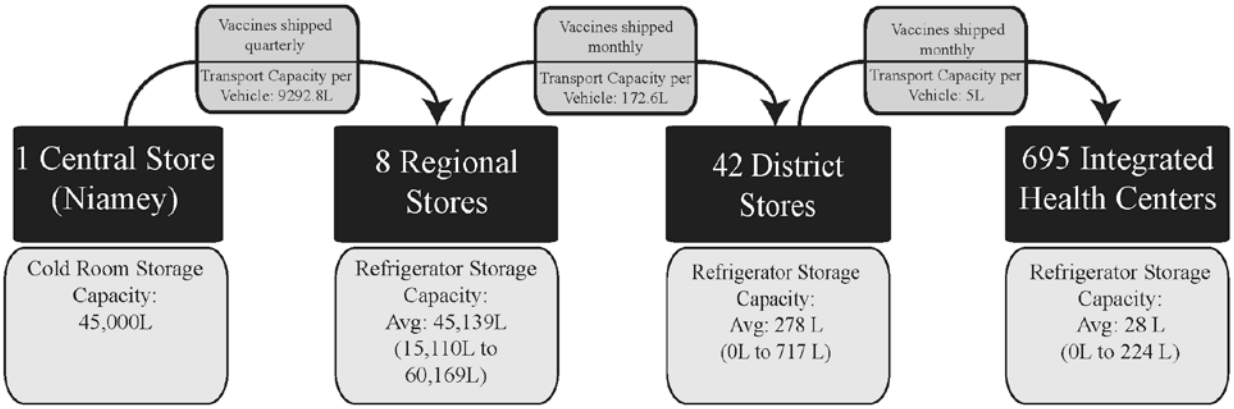

Figure 1. Niger Vaccine Supply Chain Network

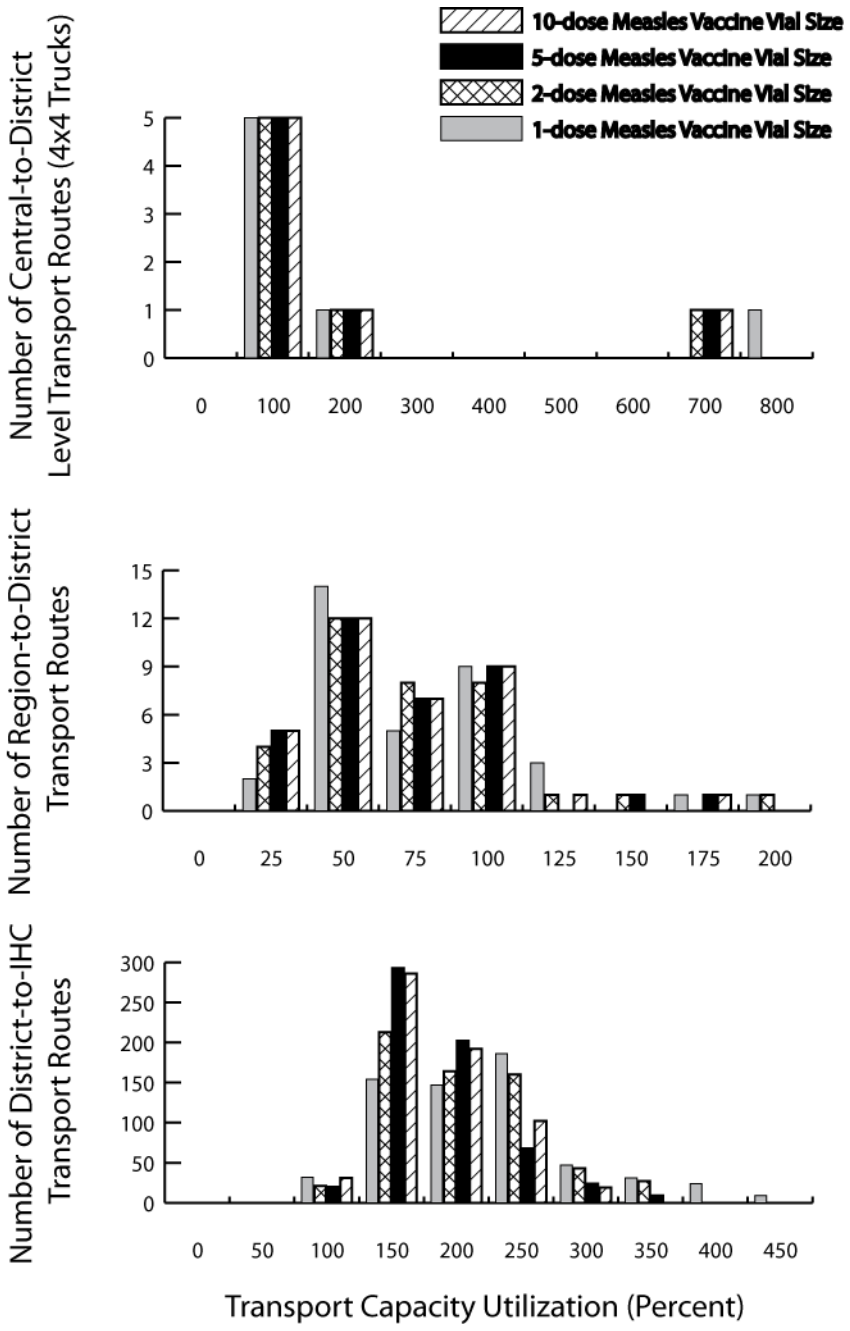

Figure 2. Truck Capacity Utilization for Multi-dose and Single-dose Measles Vaccine Presentations

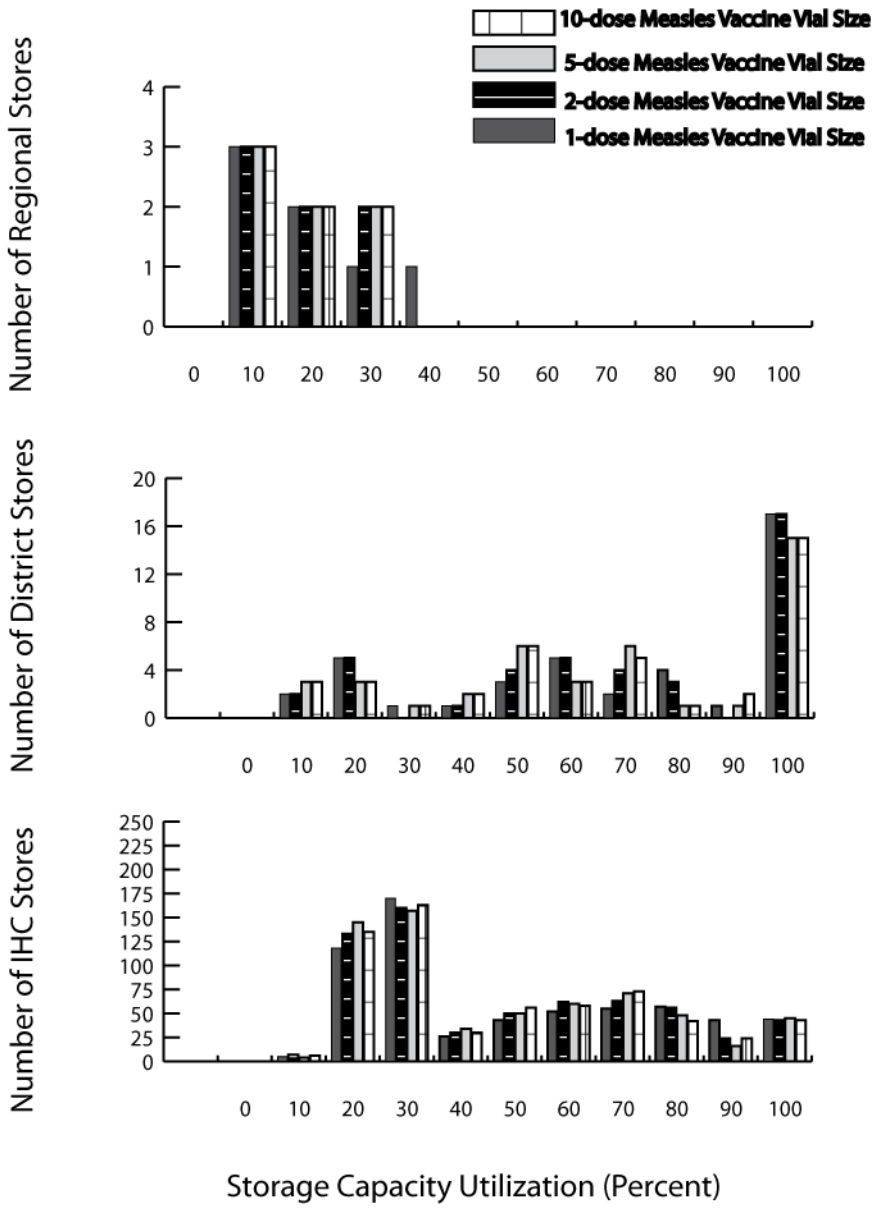

Figure 3. Storage Capacity Utilization for Multi-dose and Single-dose Measles Vaccine Presentations

2.9 TABLES

Table 1. Niger's EPI Vaccine Characteristics

Expanded Programme on Immunization (EPI) Vaccine	Immuniza-tion schedule	Doses per person	Doses per vial	Pack-aged volume per dose (cm^3)	Pack-aged volume per diluent (cm^3)	Pre-ferred storage	Source
Bacille Calmette-Guerin (BCG)	Birth	1	20	1.2	0.7	Refri-gerator	[65, 66, 90]
Diptheria-tetanus-pertussis-hepatitis B-haemophilus influenza type B (DTP-HepB-Hib)	6, 10, 14 weeks	3	1	16.8	None	Refri-gerator	[65, 66, 90]
Yellow Fever (YF)	9 months	1	10	2.5	6.0	Refri-gerator	[65, 66, 90]
Oral Polio Virus (OPV)	Birth, 6, 10, 14 weeks	4	20	1.0	None	Freezer	[65, 66, 90]
Tetanus Toxoid (TT)	1^{st} contact, 4 weeks, 6 months, 1 year	5	10	3.0	None	Refri-gerator	[65, 66, 90]
Measles (M)	9 months	1	10	2.6	0.5	Refri-gerator	[65, 66, 90]
Measles (M)*	9 months	1	5	5.2	0.5	Refri-gerator	[65, 66, 90]
Measles (M)*	9 months	1	2	13.1	0.5	Refri-gerator	[65, 66, 90]
Measles (M)*	9 months	1	1	26.1	0.5	Refri-gerator	[65, 66, 90]

Table 2. Cost Inputs for Vaccine Variables

Variable	Mean	Min	Max	Source
Cost per dose of vaccine ($US)				
Measles 10 dose	0.246	-	-	[69, 91]
Measles 5 dose	0.45	0.405	0.495	[69, 91]
Measles 1 dose	0.943	-	-	[69, 91]
Volume per dose of vaccine (cm3)				
Measles 10 dose	2.460	2.214	2.706	[69]
Measles 5 dose	5.220	4.698	5.742	[69]
Measles 1 dose	26.110	23.499	28.721	[69]
Weight of vaccines and vaccine accessories (g)				
10 dose vial (empty)	3.522	3.169	3.874	[69]
5 dose vial (empty)	2.517	2.2653	2.7687	[69]
1 dose vial (empty)	1.713	1.542	1.885	[69]
Reconstitution syringe	6.625	5.967	7.293	[69]
Injection syringe	6.625	5.967	7.293	[69]
Cost of medical vaccine accessories (2009 $US) and waste disposal (2004 $US) adjusted to 2010 $US				
Waste disposal cost per kg	6.850	2.066	10.830	[68, 69, 90]
Waste disposal cost per g	0.0069	0.0021	0.0108	[68, 69, 90]
Injection syringe	0.07	-	-	[68, 69, 90]
Reconstitution syringe	0.06	-	-	[68, 69, 90]

Table 3. Vaccine Availability across Measles Vaccine Vial Size Scenarios and Target Population Sizes

Measles Vaccine Vial Size Scenario	10-doses per vial	5-doses per vial	2-doses per vial	1-doses per vial
100% Target Population Size				
Bacille Calmette-Guerin Tuberculosis (BCG)	79%	79%	78%	76%
Diptheria-tetanus-pertussis-hepatitis B-haemophilus influenza type B (DTP-HepB-Hib)	84%	84%	82%	80%
Measles	90%	87%	86%	80%
Oral polio (OPV)	80%	80%	78%	76%
Tetanus toxoid (TT)	84%	84%	83%	80%
Yellow fever (YF)	79%	79%	78%	76%
80% Target Population Size				
BCG	84%	85%	85%	84%
DTP-HepB-Hib	86%	86%	86%	84%
Measles	94%	92%	89%	84%
OPV	80%	80%	80%	79%
TT	86%	86%	86%	84%
YF	84%	85%	85%	84%
60% Target Population Size				
BCG	81%	81%	81%	80%
DTP-HepB-Hib	91%	91%	91%	89%
Measles	93%	91%	91%	90%
OPV	82%	82%	82%	82%
TT	90%	90%	90%	89%
YF	81%	81%	81%	80%

3.0 IMPACTS OF REMOVING THE REGIONAL LEVEL FROM THE NATIONAL VACCINE SUPPLY CHAIN IN NIGER

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3.1 ABSTRACT

3.1.1 Background

Niger is considering streamlining their vaccine supply chain to improve system performance and reduce wasted vaccines and costs of supply chain storage, transport and human resources. These benefits depend on implemented shipping policies and the routing network between supply chain levels.

3.1.2 Methods

To determine the impacts of different distribution strategies, we developed a detailed discrete-event simulation model of the vaccine supply chain representing every Expanded Program on Immunization (EPI) vaccine, storage facility, cold storage equipment (e.g., cold room, refrigerator or freezer), and transport device (e.g., cold trucks, 4x4 trucks, and vaccine carriers) in the Niger Expanded Program on Immunization (EPI). Niger has a four-tiered supply chain including central, regional, district and integrated health center (IHC) levels. Experiments simulated the impact of removing the regional level and implementing either collection-based or delivery-based shipping policy from the central to district level. Additional scenarios evaluated increasing the shipping frequency from quarterly to monthly, and the number of routes from the central store from three to eight.

3.1.3 Results

Removing the regional level and implementing a collection-based shipping policy from the district level increases vaccine availability from an average of 92% at baseline (four-tiered supply chain) to 100%. Alternatively, implementing a delivery-based shipping policy from the central store on a monthly schedule in a three-route and eight-route scenario decreases vaccine availability to 87% and 91%, respectively. Restricting vaccine shipments to a quarterly schedule from the central store for the three-route and eight-route scenario reduces vaccine availability further to 58% and 61%, respectively. The collection-based shipping policy from the district level reduces the supply chain cost per arriving patient from $US0.41 at baseline to $US0.34 after removing the regional level.

3.1.4 Conclusions

Removing the regional level from the Niger vaccine supply chain can improve and worsen supply chain performance. To achieve equivalent or greater vaccine availability without the regional level compared to the currently operating four-tiered supply chain, collection-based shipments from the district to central level would need to occur at least twice per month to account for the smaller size of district 4x4 trucks compared to larger central level cold trucks.

3.2 INTRODUCTION

A vaccine supply chain is the series of steps required to get vaccines from their manufacturers to their target patients. Many vaccine supply chains involve a greater than necessary number of

steps (e.g., unnecessary levels, or locations within a level) to get vaccines from their manufacturers to clinics for administration, which may reduce the efficiency of vaccine distribution or increase vaccine wastage[1]. Vaccines in national immunization programs (NIPs) are often wasted and never reach their target population due to (1) excessive exposure to low or high temperatures[92, 93], (2) expired vials through overstocking of vaccines[94], (3) breakage due to mishandling in storage and transport[95] or (4) incomplete use of multi-dose vials[32, 96].

Streamlining vaccine supply chains is under consideration and application in several countries including Mozambique, Malawi, and Zambia, and is currently being tested in Senegal and Tunisia[1, 97]. A case study from Zambia showed that streamlining the delivery of medicines to health centers reduced the frequency at which clinics ran out of basic medicines[98].

Reducing the number of steps in a supply chain, a strategy known as “streamlining”, that are required to get vaccines from their manufacturers to patients, can reduce risks wastage due to handling or expiration, delays in delivery, and potentially operational costs from maintaining redundant storage facilities and inefficient transport routing networks. Moreover, removing a level in the vaccine supply chain brings vaccines closer to patients arriving at IHCs and allows the supply chain to be more responsive to sudden unanticipated surges in vaccine requirements (e.g., vaccines required for disease outbreaks, unexpected losses from equipment breakdown, etc.)[99]. However, removing intermediate storage facilities can increase the shipment distances and may therefore, increase the costs and risks of breakage in transport. Removing a level may also require the re-structuring of distribution routing networks, shipping frequencies and the order in which warehouses and clinics are supplied.

To evaluate these tradeoffs, the Vaccine Modeling Initiative (VMI), a Bill and Melinda Gates funded project to build computational models for better understanding the dynamics of vaccine distribution in low and middle-income countries, has been working with collaborators in Niger to develop models for the national vaccine supply chain. In an effort to better understand the potential advantages and disadvantages of streamlining vaccine supply chains, the VMI evaluated the removal of the regional level from the vaccine supply chain in Niger.

3.3 METHODS

3.3.1 Model Description

The VMI constructed a model representing the vaccine supply chain in Niger. HERMES – the Highly Extensible Resource for Modeling Event-driven Simulations – is a dynamic, custom-designed, discrete event simulation model developed in the programming language Python, using resources provided by the SimPy package[60]. This model simulates all of the operational policies, storage and administering facilities, transport procedures and resources, personnel and equipment in the Niger vaccine supply chain, while also accounting for stochastic variations in the system (i.e., likelihood of vial breakage from handling during storage or transport). This model represents the flow of all World Health Organization (WHO) Expanded Program on Immunization (EPI) vaccines from the level of the manufacturer, to the central storage facility in Niamey, Niger, through each subsequent level of the supply chain, and finally to the vaccine recipients at the health center level.

3.3.2 Description of the Niger Vaccine Supply Chain

Niger's vaccine supply chain is comprised of the following four levels: national, regional, district, and IHC, as illustrated in Figure 1. Vaccines arrive at the central storage facility (cold room capacity=45,000 Liters) in Niamey, the capital of Niger, by way of the United Nations Children's Fund (UNICEF) in Copenhagen and various intermediaries, and then subsequently move to seven of the eight regional storage facilities (average cold room and refrigerator capacity=45,139 Liters, range: 15,110-60,169 Liters), forty-two district storage facilities (average refrigerator capacity=278 Liters, range 0-717 Liters), and six hundred and ninety five integrated health center (IHC) storage facilities (average refrigerator capacity=28 Liters, range: 0-224 Liters) within the country. The eighth regional store is non-functional and thus, district stores that would normally be served by the eighth regional stores travel to the central store directly to procure their vaccines using their own 4x4 trucks. Vaccine administration occurs at the IHC level four days per week. The majority of the supply chain locations are located in the southern belt of the country and within the vicinity of population settlements, and as expected there is variability in the transport distances (hours traveled) between these various vaccine supply chain locations.

Data were collected from several sources to construct the framework for the model, including (1) the WHO in Geneva, (2) the WHO in Niger, (3) UNICEF in Niger, (4) the Niger National Geographic Institute (NGI), (5) the Niger Ministry of Health (MOH), (6) the WHO EPI in Niger, (7) and from direct in-country field observations involving interviews and surveys of cold chain personnel. In 2009, the following data were collected from these sources to begin model development: cold chain equipment inventory; transport resources; operating polices for

shipments, storage, and aspects of vaccine administration; patterns of patient arrival rates; and personnel capacity.

The number and type of vaccines administered at the IHCs is a function of the population demand drawn from birth registry data aggregated at the district level from a 2005 survey (557,381 total newborns across all districts) which has been adjusted to 2010 (586,880 total newborns across all districts) to account for a 1.04% population growth rate[62]. These newborns are distributed across each of the IHC sites, and in each of the immunization sessions per month. Every time a child arrives at a vaccination IHC, he or she receives the appropriate age-specified (newborn to 11 months old, and 12 to 24 months old) vaccines if there is enough doses on-hand.

3.3.3 Structure of the Model

Every storage location, refrigerator, freezer, and transport vehicle in the Niger vaccine supply chain is represented in HERMES, including the specific number of refrigerators and freezers and their specified volumes for each location using data from cold chain equipment inventories. Each freezer is designed and assumed to maintain a temperature of -15°C to -25°C and each refrigerator a temperature of 2°C to 8°C. Each vaccine's recommended temperature profile determines which compartment it will be stored in, the freezer or refrigerator.

The model computes the vaccine inventory (i.e., the number of vaccines currently stored in that refrigerator or freezer) in each cold room, freezer or refrigerator (equation 1). The current vaccine inventory is equal to the number of vaccines left over from the day before minus the number of vaccines that are removed for distribution or administration, plus the number of vaccines that arrive that day:

[1] $Vaccine\ Inventory\ for\ a\ given\ Refrigerator\ or\ Freezer\ on\ Day\ t$

$$= (Vaccine\ present\ on\ day\ t-1) + (Vaccines\ added\ on\ day\ t)$$
$$- (Vaccines\ removed\ on\ day\ t) - (Vaccines\ administered\ on\ day\ t)$$
$$- (Vaccine\ open\ vial\ waste)$$

The number of vaccine doses removed for administration on a given day includes the number of doses wasted from open vial waste (i.e., doses that are discarded from incompletely consumed vials). The model does not allow the total vaccine inventory stored at any one time in a cold room, freezer, or refrigerator to ever exceed that device's storage capacity. Similarly, vaccine shipments from location to location cannot contain more vaccine vials than the specified storage capacity of that particular transport vehicle or device and occur at defined frequencies specific to the transportation route. Vaccines in Niger are transported in two cold trucks (available transport space=9,292.8L) from the central level to the regional level, cold boxes in 42 4x4 trucks (172.6L) from the regional level to the district level, and vaccine carriers (5.0L) carried by public health workers on foot or on motorbikes from the district level to the 695 IHC level stores. Distribution of the vaccines from the central to the regional level occurs in two loops sequentially servicing the seven regional storage facilities. The districts in the eighth region, which has a non-operational regional store, procure vaccines directly from the central store. All regional-to-district and district-to-IHC vaccine distribution occurs through direct point-to-point shipments (e.g., one storage facility directly collects vaccines from another) if and when vaccines are needed. Based on country-policy, collections from the lower two levels occur monthly on average, but the model allows for up to one shipment per week for resource-constrained locations.

Three types of vaccine loss are accounted for in the model:

- Shipping loss: the proportion of vaccines wasted during transport from excessive temperature exposure, expiration or breakage each day.
- Inventory loss: the proportion of vaccines wasted during storage from temperature exposure (e.g., below 2°C or above 8°C), expiration or breakage each day.
- Open vial loss: the proportion of unused doses of vaccine from vials that are opened but not completely consumed before expiration (e.g., only three doses used from a ten-dose vial) as detailed by a previously published study and the WHO's Multi-Dose Vial policy (MDVP)[64, 96].

3.3.4 Vaccine Characteristics

The Niger supply chain model contains the six current routine WHO EPI vaccines. The vaccines' packaged volumes (the total volume of the vaccine, container and packaging that occupies space in the cold room, freezer, or refrigerator), listed in Table 1, are taken from the WHO's standard vaccine product information provided in the 2009 Vaccine Volume Calculator and Prequalified Vaccines Database[66, 67]. Vaccine packaged volumes were used to determine the space required for vaccine storage and transport in the supply chain. The volumes of the diluents are also accounted for in HERMES. Diluents only consume space in the storage devices at the IHC locations a day prior to vaccine administration.

3.3.5 Supply Chain Performance Indicators

The supply ratio was computed in each simulation for of each vaccine type at each IHC and is a proxy for vaccine availability at a vaccine administering location (equation 2).

$$[2]\ \boldsymbol{Vaccine\ Supply\ Ratio} = \frac{Number\ of\ patients\ receiving\ vaccine\ per\ day}{Number\ of\ patients\ arriving\ at\ a\ clinic\ per\ day}$$

The transport capacity utilization rate (equation 3) for each transport device (e.g., the amount of space consumed by vaccines, diluents, and accessories in trucks, cold boxes or vaccine carriers) and the storage capacity utilization rate (equation 4) for each device was computed in each simulation run:

$$[3]\ \boldsymbol{Transport\ Capacity\ Utilization} = \frac{\text{Transport space consumed per shipment (L)}}{\text{Total available transport space per shipment (L)}}$$

$$[4]\ \boldsymbol{Storage\ Capacity\ Utilization} = \frac{\text{Storage space consumed per time period (L)}}{\text{Total available storage space per time period (L)}}$$

Table 2 lists input values used to compute storage, building facility, transport and human resources costs, which are commonly-used cost components of supply chain economic analyses in healthcare settings[40, 100, 101]. Data to compute these costs came from the 2005 Niger Comprehensive Multi-year Plan (cMYP) and the Cold Chain Equipment Inventory[91]. A generally accepted discounted rate of 3% updated costs to 2011 United States dollars ($US)[70]. Only a subset of the economic components used to compute the total annual costs for the routine

immunization program in Niger were considered in this analysis and are outlined in equation 5 for the total cost per anticipated dose administered per year:

$$[5]\ \boldsymbol{Cost\ per\ Anticipated\ Dose\ Delivered}$$
$$= (Recurring\ costs\ of\ cold\ storage\ equipment$$
$$+ Recurring\ costs\ of\ supply\ chain\ buildings + Recurring\ costs\ of\ transport$$
$$+ Recurring\ costs\ of\ human\ resources + Capital\ costs\ of\ new\ storage\ devices$$
$$+ Capital\ costs\ of\ new\ transport\ devices$$
$$+ Capital\ costs\ of\ new\ building\ infrastructure) Recurring\ costs\ of\ cold\ storage\ equipment$$
$$+ Recurring\ costs\ of\ supply\ chain\ buildings + Recurring\ costs\ of\ transport$$
$$+ Recurring\ costs\ of\ human\ resources + Capital\ costs\ of\ new\ storage\ devices$$
$$+ Capital\ costs\ of\ new\ transport\ devices$$
$$+ Capital\ costs\ of\ new\ building\ infrastructure$$
$$\div Number\ of\ anticipated\ doses\ delivered\ per\ arriving\ patient\ at\ each\ IHC$$

Equipment for storage in Niger is housed in facilities not exclusively devoted to the EPI and building costs are often shared. Therefore only the costs of operating buildings and storage equipment devoted to the EPI are considered. The cost of storing vaccines was computed in equations 6 and 7 and summed for all locations in each level:

[6] ***Recurring Costs of Supply Chain Storage Equipment***

$$= Number\ of\ equipment\ type\ by\ location$$
$$\times [Equipment\ energy\ costs\ per\ year(\$US)$$
$$+ Equipment\ depreciation\ cost\ (\$US)$$
$$+ Equipment\ maintenance\ cost\ per\ year(\$US)]$$

[7] ***Recurring Costs of Supply Chain Buildings***

$$= Number\ of\ building\ type\ by\ location \times [Building\ energy\ costs\ per\ year(\$US)$$
$$+ Building\ depreciation\ cost(\$US) + Building\ maintenance\ cost\ per\ year(\$US)]$$

The cost of transporting vaccines was computed in equation 8 and summed for all routes between each level:

[8] ***Recurring Costs of Transport***

$$= Number\ of\ vehicle\ type\ by\ location$$
$$\times [Vehicle\ cost\ of\ fuel\ per\ year(\$US)$$
$$+ Vehicle\ depreciation\ cost\ per\ year\ (\$US)$$
$$+ Vehicle\ maintenance\ cost\ per\ year(\$US)]$$

The fuel efficiency for each vehicle type, maintenance cost rates, and the years of useful life for corresponding annualization factors were specified by the Niger cMYP[91].

The cost of human resources was computed in equation 9 and summed for all location at each level:

[9] $\boldsymbol{Recurring\ Costs\ of\ Human\ Resources}$

$$= Number\ of\ personnel\ type\ by\ location$$

$$\times Proportion\ of\ their\ time\ devoted\ to\ EPI\ activities$$

$$\times [Salary\ per\ year(\$US) + Benefits\ per\ year(\$US)]$$

The number, names and geographic locations (i.e., longitude and latitude coordinates) of central, regional, district, and IHC cold chain facilities were established from the 2008 Niger cold chain equipment inventory. Distances travelled between these locations were computed by triangulating location coordinates from (1) health facility coordinates in Niger from the WHO Cold Chain Equipment Inventory, (2) population settlement coordinates from the United Nations Food and Agriculture Organization (FAO)[102], and (3) coordinates from GeoNames Geographical Database[103] for Niger. Multiple sources were used to triangulate the location coordinates for validation purposes and to reconcile differences in the spelling of location names.

Using ArcGIS software version 9.0 (ESRI Inc., Redlands, CA)[104], we used the administrative boundaries (i.e., country, regional and district borders) provided within the NGI datasets coupled with the located coordinates and road networks from the Africa Infrastructure Country Diagnostics (AICD) Roads and Utilities Survey[105]. With the ArcGIS Network Analyst extension 9.3 (ESRI Inc., Redlands, CA)[106], we calculated the shortest distance in kilometers between locations at different levels in the cold chain (central-to-regional, or central-to-district stores). All locations fell within 2 miles of the road network.

3.3.6 Shipping policy Scenarios

As illustrated in Figure 1, multiple scenarios without regional stores were modeled and compared to the baseline Niger vaccine supply chain model which contains representations of all seven regional stores. Monthly shipping frequencies imply vaccines are shipped from location to location each month, whereas quarterly shipping frequencies occur once every three months.

- Baseline: central store delivers vaccines in two shipping loops to seven regional stores quarterly, from which each district procures its own vaccines, as shown in Figure 1.
- Shipping policy 2: district stores collect vaccines directly from the central store as needed and when vaccines at the central store are available.
- Shipping policy 3: the central store distributes vaccines directly to the district stores in three cold trucks along three shipping loops on a monthly shipping frequency.
- Shipping policy 4: the central store distributes vaccines directly to the district stores in three cold trucks along three shipping loops on a quarterly shipping frequency.
- Shipping policy 5: the central store distributes vaccines directly to the district stores in eight cold trucks along eight shipping loops on a monthly shipping frequency.
- Shipping policy 6: the central store delivers vaccines directly to district stores in eight cold trucks along eight shipping loops on a quarterly shipping frequency.

Vaccine shipments between the district and IHC stores in all scenarios occur as necessary with a maximum shipping frequency of once per week. The shipping loops in policies 3-6 were selected to mimic the original routing network in the baseline scenario, which are defined based on existing administrative boundaries, and local knowledge of road conditions (i.e., all-season roads versus unpaved paths) and accessibility.

3.3.7 Sensitivity Analyses

Sensitivity analyses systematically ranged the following parameter: inventory loss rate (range: 0-3%), shipping loss rate (range: 0-3%), storage capacity utilization (85-100%), and population demand (static demand which means the number of patients in a month is fixed based on projected population estimates and does not fluctuate from month to month versus dynamic monthly distribution, which means the number of vaccine recipients in a given month draws from a Poisson distribution with a mean of (λ)). It is typically difficult to estimate closed vial wastage, which is the wastage of vaccine before a vial is opened, in shipping and storage because these rates are seldom reported separately from open vial waste and may sometimes stem from vaccine mismanagement. Communications with vaccine logistics experts suggested 1% inventory and shipping loss rates. We then additionally explored 2% and 3% loss rates in sensitivity analyses. Each scenario was simulated and averaged over ten replications.

3.4 RESULTS

Sensitivity analyses demonstrated that varying the patient demand (static versus dynamic), shipping and inventory loss, and storage capacity utilization did not notably affect the pattern of results. Therefore, the following results report from scenarios representing 1% inventory and shipping loss, 100% capacity utilization, and dynamic monthly demand.

3.4.1 Overall Impact

Our model results suggest that removing the regional level in the Niger vaccine supply chain can improve vaccine availability if either districts collect vaccines directly from the central store or if cold trucks deliver vaccines from the central store to the districts on a monthly schedule. Policies in which the shipping frequencies of cold trucks from the central store are quarterly, negatively impact vaccine availability. Removing the regional level also reduces recurring costs of vaccine storage, transportation and human resources.

3.4.2 Impact on Vaccine Administration

At baseline (current 4-tiered supply chain), the vaccine availabilities of the tuberculosis, diphtheria-tetanus-pertussis-hemophilus influenzae type B-hepatitis B, oral polio, yellow fever, measles and tetanus toxoid vaccines were 89%, 93%, 92%, 89%, 95% and 93%, respectively. Implementing policy 2 in which the district stores bypass the regional level and collect vaccines directly from the central store increases vaccine availability from an average of 92% at baseline to 100% when vaccine shipments are made at least. Alternatively, implementing policy 3 and 5 in which the central store delivers vaccines in 3 and 8 shipping loops directly to district stores monthly decreases vaccine availability from 92% at baseline to 87% and 91%, respectively. Moreover, implementing policies 4 and 7, in which the shipping frequency from the central store is maintained at four times per year, as in the baseline policy, in 3 and 8 shipping loops, decreases vaccine availability further from 92% at baseline, to 58% and 61%, respectively. In a completely collection-based system, vaccines could be collected in the right quantity and at the right time, resulting in less open vial waste and fewer missed vaccination opportunities. In a completely

distribution-based system, vaccines are shipped in predetermined cycles and amounts, which reduces the supply chain's flexibility in meeting unanticipated surges in vaccine needs or results in excess vaccines on hand. These subtle changes are difficult to discern without a dynamic model.

Thus, removing the regional level can both improve and reduce vaccine availability. policy 2, wherein districts collect vaccines from the central store, outperforms other policies. Limiting the number of shipments districts can make in one month to 3, 2 and 1 shipments in some cases, however, changes the average vaccine availability from 100% to 100%, 97% and 90%, respectively, suggesting that removing the regional level can only be more effective than the baseline shipping policy if districts have the capacities (i.e., human resources, transportation, etc.) to collect vaccines at least twice a month.

3.4.3 Impact on Vaccine Transport

Figure 5 shows the transport capacity utilization across vaccine shipping policy scenarios. At baseline, the average transport capacity utilizations from the central to regional level (cold truck), regional to district level (4x4 truck), and district to IHC level (vaccine carrier) were 66% (range: 59-73%), 64% (range: 4-616%) and 147% (range: 60-237%). The ranges reported are ranges of transport capacity utilization across vehicles in a level. Many of the transport routes at baseline are overfilled, which indicates that portions of vaccine shipments could not be met, or the total volume of requested vaccines did not fit inside the shipment container. Outstanding vaccine orders would be delivered in a following shipment. If this shipment was the last vaccine shipment in the month or in the period, the remaining vaccine orders go unmet, resulting in vaccines not being available for arriving patients.

Implementing policy 2 in which districts stores bypass the regional level and collect vaccines directly from the central store decreases the transport capacity utilization across all 4x4 trucks from 64% (range: 4-616%) at baseline to 46% (range: 4-116%), and in vaccine carriers from the district to IHC level from 147% (range: 60-237%) at baseline to 138% (range: 53-242%).

Implementing policies 3 and 4, in which vaccines are delivered by cold trucks from the central store directly to district stores in 3 shipping loops either monthly or quarterly also reduces transport capacity utilization across all cold trucks from 66% (range: 59-73%) at baseline to 17% (range: 12-21%) and 27% (range: 18-35%), respectively. Similarly, implementing policies 5 and 6 in which vaccines are delivered directly from the central store to district stores in 8 loops by cold trucks either monthly or quarterly decreases transport capacity utilization to 6% (range: 2-11%) and 10% (range: 4-19%), respectively.

The transport capacity utilization of shipments between the district and IHC level decreased for shipping policy 2 from 147% (range: 60-237%) at baseline to 138% (range: 53-242%) and 157% (range: 79-300%), respectively. Shipping policies 3, 4, 5 and 6 increased transport capacity utilization between district and IHC stores to 162% (range: 78-299%), 188% (range: 91-303%), 156% (range: 80-300%) and 185% (range: 92-303%), respectively.

Due to the high variability across sites in a level (an effect largely driven by population variation from site to site), the transport capacity utilization from the central store to the district stores and from the district stores to the IHC's in box and whisker plots (Figures 6 and 7, respectively). Figure 8 shows the transport capacity utilization across vaccine shipping policy scenarios.

3.4.4 Impact on Vaccine Storage

Figure 9 shows the average vaccine storage capacity utilization across all locations within a level. Implementing shipping policy 2 in which district stores collect vaccines directly from the central store increases storage capacity utilization at the central and district levels from 65% and 64% (range: 3-100%) at baseline to 76% and 65% (range: 3-100%), respectively. The ranges reported are ranges of storage capacity utilization across locations in a level. Implementing shipping policies 3 and 4 in which vaccines are delivered in 3 shipping loops from the central to district level monthly or quarterly also increases central and average district level storage capacity utilization to 67% and 89% (range: 0-100%), and 93% and 88% (range: 1-100%), respectively. Finally, implementing shipping policies 5 and 6 in which vaccines are delivered from central to district level in 8 shipping loops also increases average storage capacity utilization at central and district levels to 67% and 89% (range: 5-100%), and 93% and 91% (range: 13-100%), respectively.

Storage capacity utilization at the IHC level decreased slightly in all scenarios from an average of 43% (range: 0-98%) at baseline to 44% (range: 5-98%), 43% (range: 5-97%), 39% (range: 2-98%), 42% (range: 2-100%) and 40% (range: 5-97%) for shipping policies 2-6, respectively.

3.4.5 Impact on Vaccine Supply Chain Costs

At baseline, the total costs, including vaccine transport ($US711,630), storage ($US133,209), building facility ($US46,382) and human resources ($US1,407,925) costs, amount to $US2,299,146 per year, which translates to $US0.34 per anticipated dose delivered over a year.

In removing the regional level, human resources and a subset of transportation costs were eliminated for all scenarios. Implementing shipping policy 2-6 reduces total annual costs to $US2,082,323 ($US0.31 per anticipated dose delivered per year), $US1,900,342 ($US0.28 per anticipated dose delivered per year), $US1,860,296 ($US0.27 per anticipated dose delivered per year), $US1,915,874 ($US0.28 per anticipated dose delivered per year) and $US1,902,432 ($US0.28 per anticipated dose delivered per year). However, in shipping policies 3-4, one new cold truck must be procured, and in shipping policies 5-6, 5 new cold trucks must be procured from the baseline inventory of 2 cold trucks. The capital costs of these additional vehicles slightly increases the cost per anticipated dose delivered per year to $US0.29, $US0.28, $US0.35 and $US0.34 for shipping policies 3-6, respectively, in the first year of policy implementation.

3.5 DISCUSSION

Results from our model show that depending on the implemented strategy, removing the regional level can both improve and worsen vaccine supply chain performance in Niger. While removing the regional level results in lowered costs per anticipated dose delivered per year, the relative cost savings depend on the implemented routing network (i.e., collection-based versus delivery-based from the central store). While shipping policy 2, in which districts collect vaccines from the central store, is slightly more costly than shipping policies 3-6, in which the central store delivers scheduled shipments to district stores in cold trucks, it provides higher vaccine availability if shipments can be made at least twice per month and reduces the cost per arriving patient compared to the costs of the current four-tiered system.

Because each delivery, collection, shelving and un-shelving procedure carries a risk of vaccine breakage, mishandling, or temperature exposure, fewer levels in a supply chain can result in reduced risks of vaccine wastage. Moreover, while having fewer levels may increase travel distance and time between sites and ultimately transportation costs (i.e., fuel costs, vehicle maintenance and depreciation), it can also result in cost savings from reductions in total annual expenditures on storage facilities, human resources and cold chain equipment, which outweighed the cost increases of longer transportation distances in our analysis.

Streamlining the vaccine supply chain can also simplify requisition and distribution logistics. Delivery-based supply chain policies (i.e., fixed volume of vaccines delivered on predetermined schedule) depend on accurate forecasts of vaccine demand at the IHC level. Without knowing how many patients will arrive at an IHC, delivery-based policies risk under-supplying or over-supplying locations that experience unexpectedly high or low patient arrival rates. Vaccine shipments distributed through collection-based supply chain policies (i.e., variable volume of vaccines collected if and when vaccines are needed) can be more closely matched to actual patient consumption. Streamlining the vaccine supply chain can also simplify distribution logistics in emergency situations (i.e., when large volumes of vaccines are unexpectedly required), by reducing the number of steps required in delivering vaccines from the central store to administering sites in a shortened timeframe.

Nevertheless, important considerations remain in determining whether streamlining a vaccine supply chain is programmatically-effective and cost-effective. For instance, depending on the implemented shipping policy, removing the regional level can lead to increases in recurring or capital costs of transportation, or to increases in storage or transport utilization in some locations which may reduce the supply chain's ability to handle unanticipated surges in vaccine demand

(e.g., due to truck breakdown, or in response to disease outbreak) or future vaccine introductions. These may require increased investments in capital resources (i.e., additional cold storage equipment or transport vehicles) and human resources (i.e., EPI logisticians and managers, nurses, drivers, etc.). Changing the supply chain structure also impacts the vaccine shipment routing network which can result in longer travel distances, times, and associated costs.

Our study illustrates the usefulness of models in determining the effects of decisions not immediately apparent. Models have widely been used by decision-makers in other industries including meteorology[75], manufacturing[74], transportation[76], aerospace[77], and finance[78], and sports and rehabilitation[79]. Their use to date in public health, however, has not been as extensive[80-82]. Models have assisted responses to health-care associated infections and infectious disease transmission such as the 2009 H1N1 influenza pandemic, however much of their potential remains untapped[83-87].

3.5.1 Limitations

Models are simplified representations of real life and therefore cannot account for every potential factor, event or outcome. The model is based on data collected up until 2010 and may not represent changes that may occur in the future. Actual demand may vary from our estimated demand, which was drawn from cross-sectional census data, although sensitivity analyses have demonstrated the effects of altering demand. Our analysis did not include all EPI cost components such as costs for disease surveillance and supplementary vaccination campaigns. Constructing our model involved substantial data collection from a wide variety of sources including records and interviews at different locations. As a result, parameter values may vary in

accuracy and reliability, although sensitivity analyses demonstrated that model outcomes are robust under a wide variety of circumstances.

3.6 CONCLUSION

Removing the regional level from the Niger vaccine supply chain can improve and worsen supply chain performance. To achieve equivalent or greater vaccine availability without the regional level compared to the currently operating four-tiered supply chain, collection-based shipments from the district to central level would need to occur at least twice per month, a policy that would also result in annual cost savings per anticipated dose delivered.

3.7 ACKNOWLEDGEMENTS

This study was supported by the Vaccine Modeling Initiative (VMI), funded by the Bill and Melinda Gates Foundation and the National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) grant 1U54GM088491-0109. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. We would also like to acknowledge the important contributions of the following individuals to our study: Dr. Amadou Garba (Schistosomiasis Control Initiative), Dr. Tiekoura Coulibaly (EPI Officer, WHO Niger),

Dr. Abdou M. Chitou (EPI Administrator, UNICEF Niger), and Mr. Harou Moussa (EPI Office, WHO Niger).

3.8 FIGURES

Figure 1: Niger Vaccine Supply Chain Network

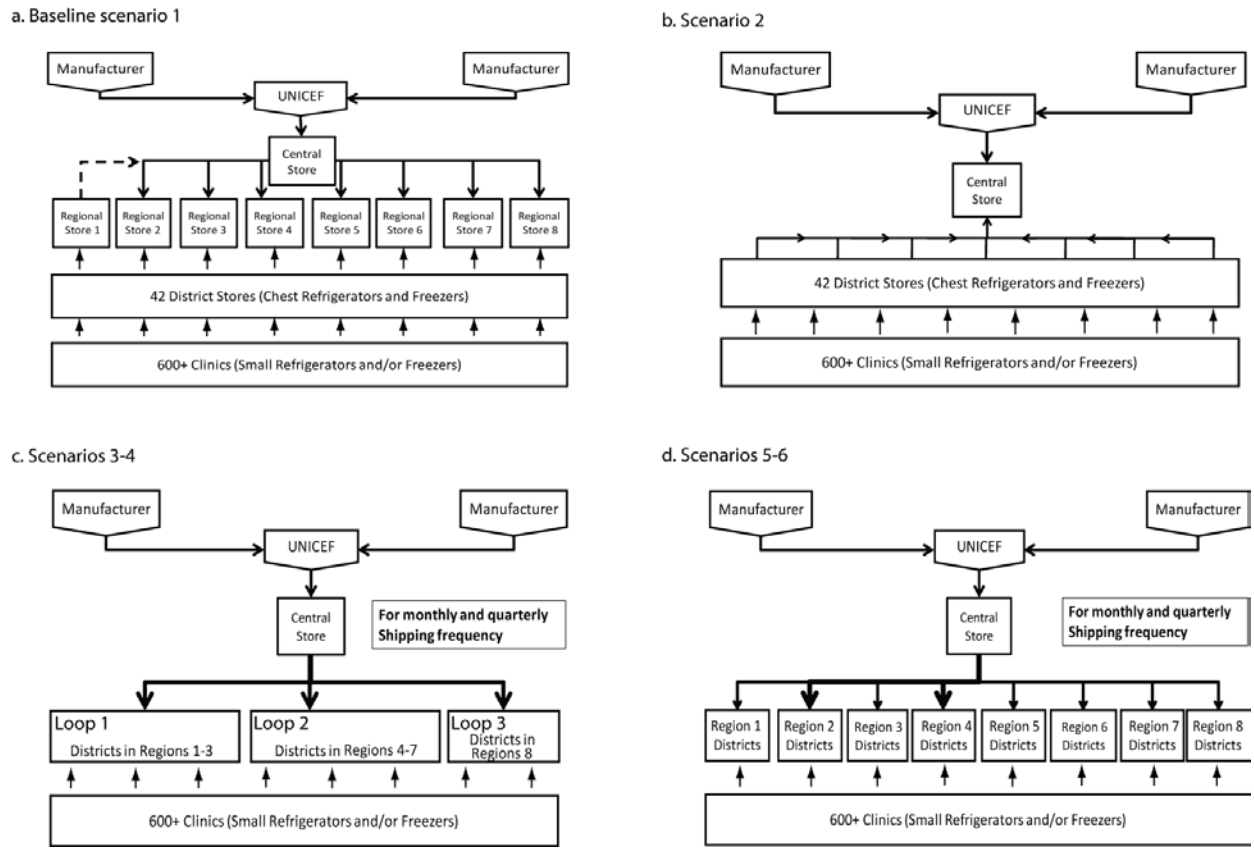

Figure 4. Niger Vaccine Supply Chain Network

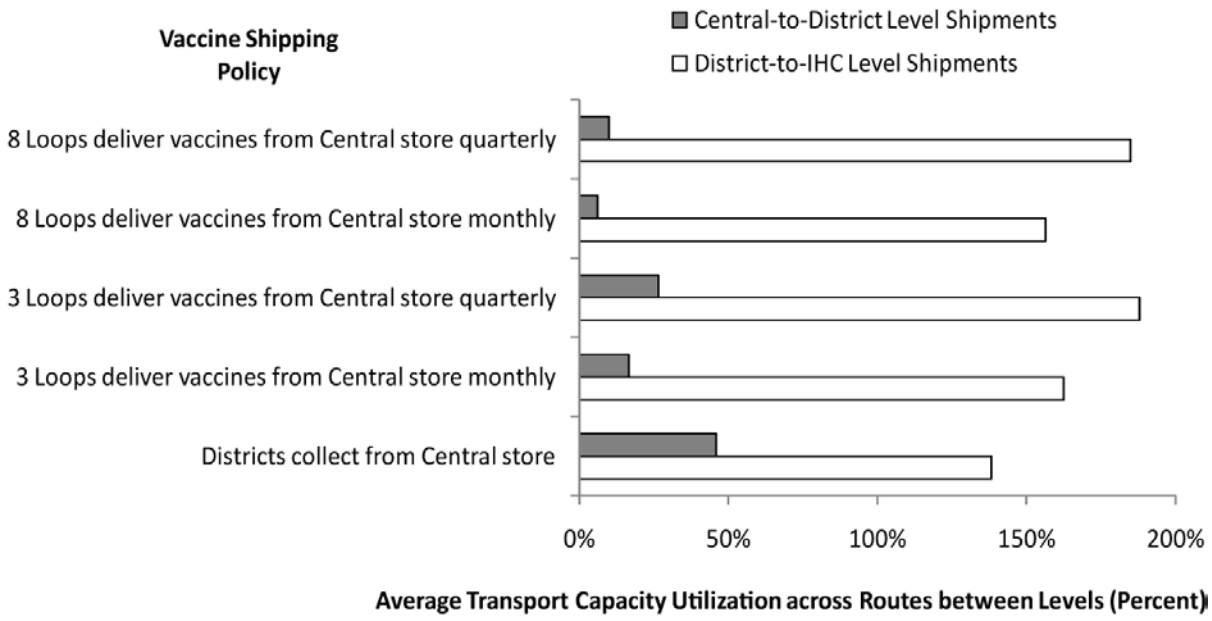

Figure 5. Average Transport Capacity Utilization across Routes between Levels by Vaccine Shipping Frequency

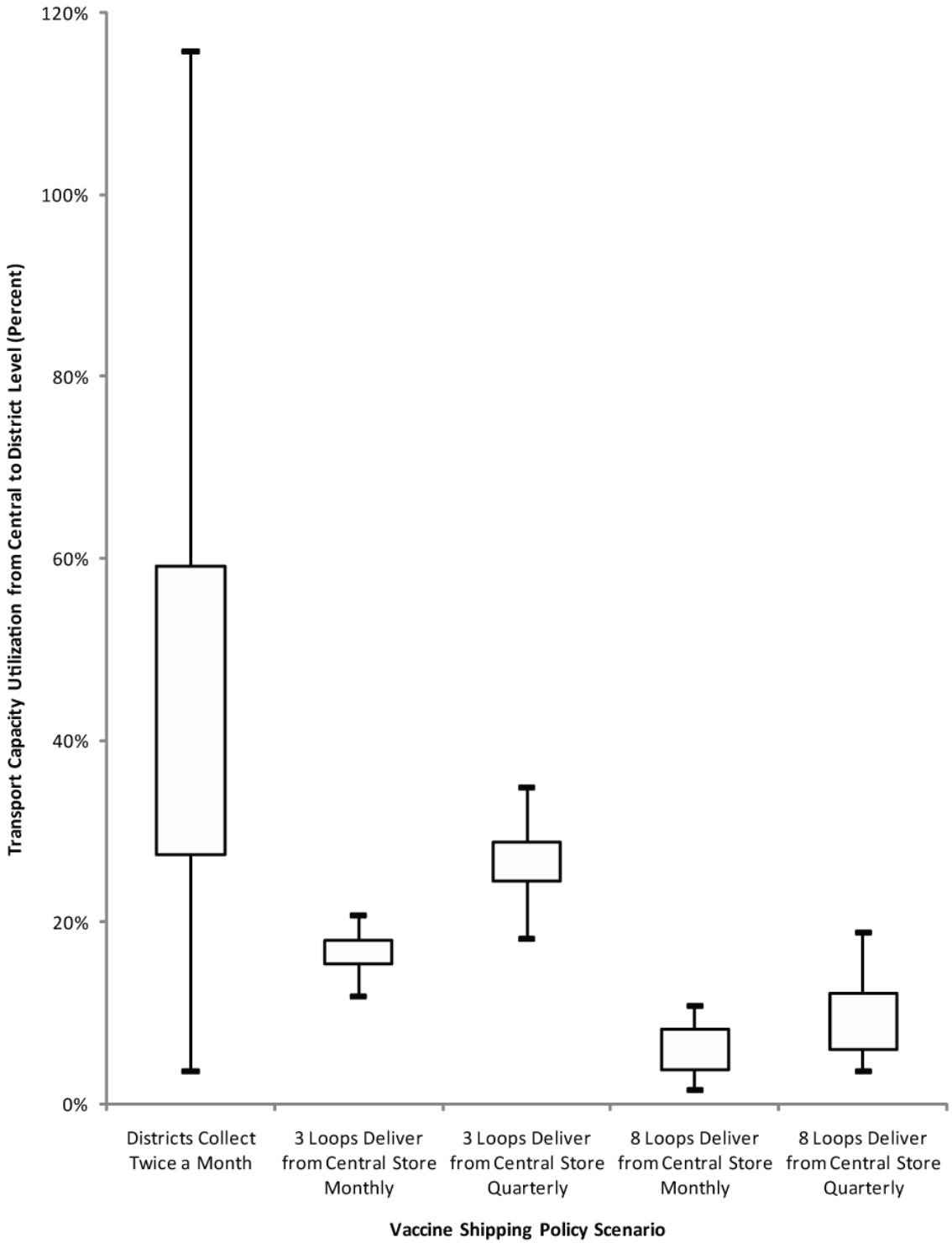

Figure 6. Box Plots of Transport Capacity Utilization from Central to District Level across Vaccine Shipping Policy Scenarios

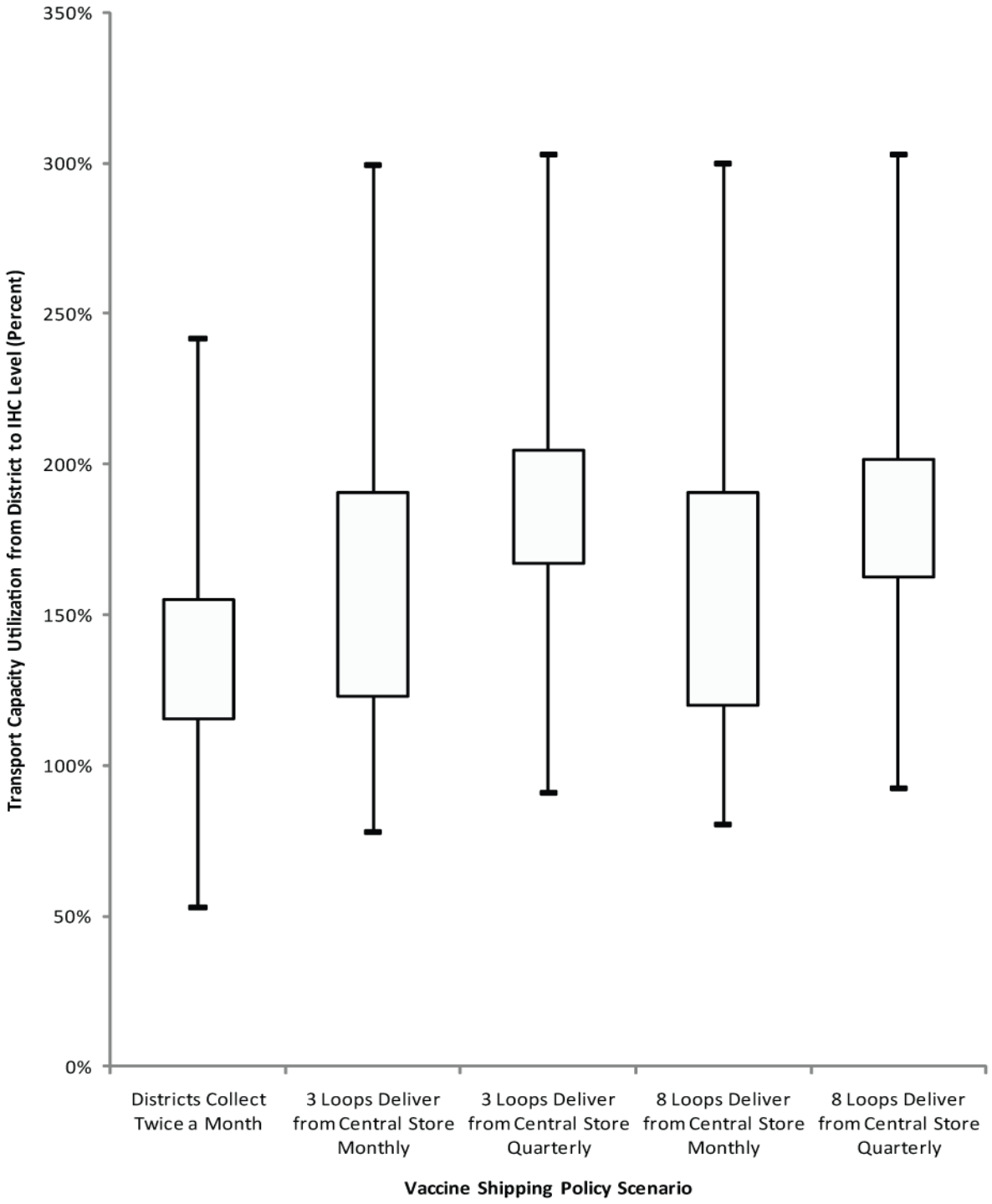

Figure 7. Box Plots of Transport Capacity Utilization from District to IHC Level across Vaccine Shipping Policy Scenarios

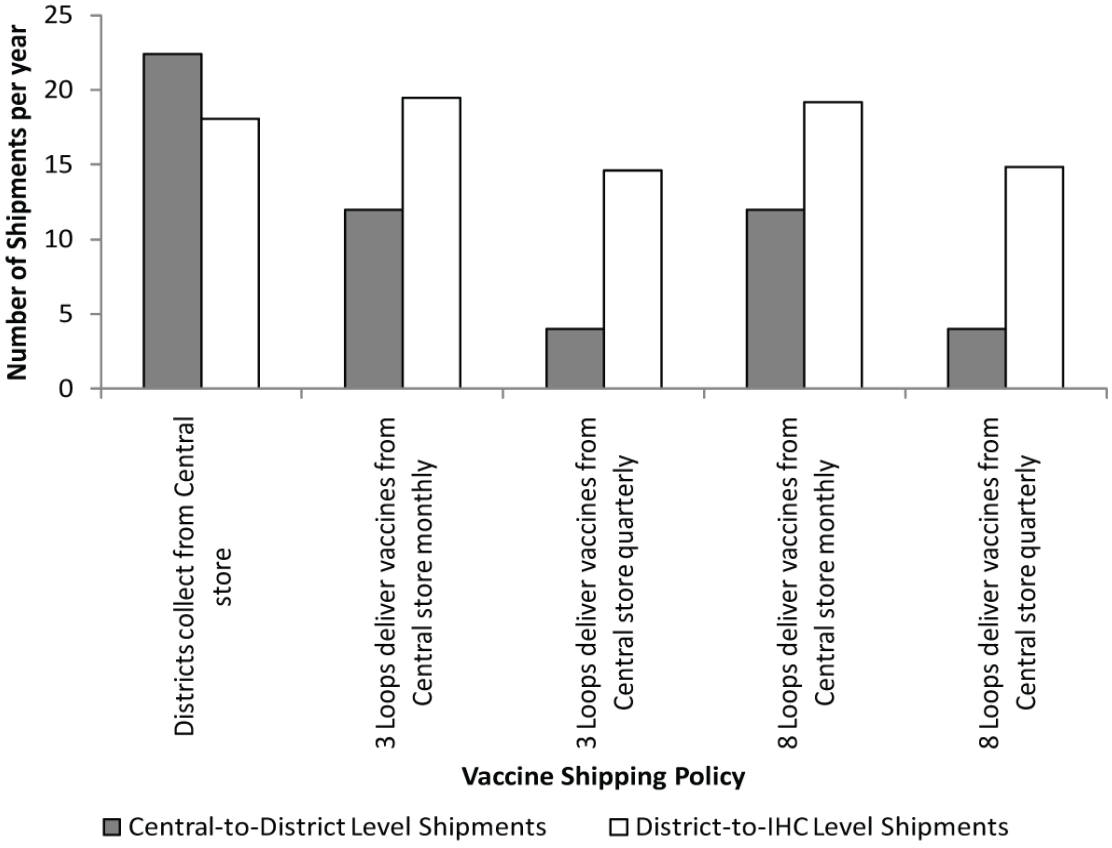

Figure 8. Average Annual Shipment Frequency by Vaccine Shipping Policy

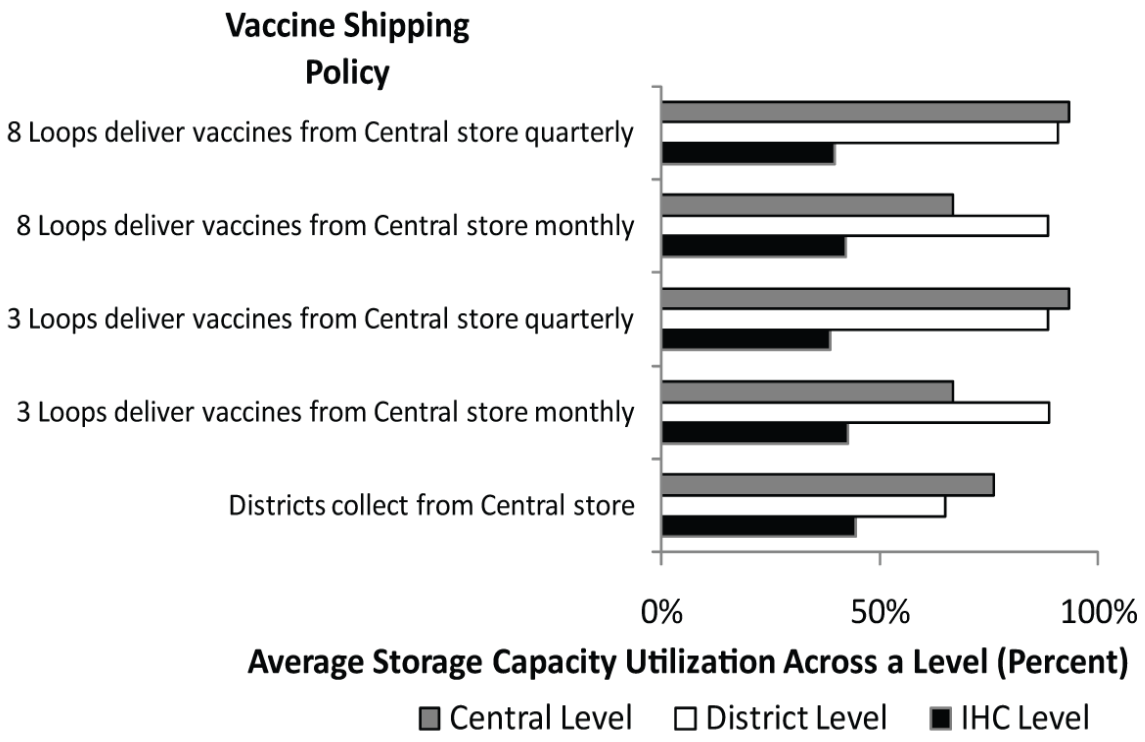

Figure 9. Average Storage Capacity Utilization by Level across Vaccine Shipping Policy Scenario

3.9 TABLES

Table 4. Niger EPI's Vaccine Characteristics

EPI Vaccine	Bacille Calmette-Guerin (BCG)	Diptheria-tetanus-pertussis-hepatitis B-hemophilus influenza type B (DTP-HepB-Hib)	Yellow Fever (YF)	Oral Polio Virus (OPV)	Tetanus toxoid (TT)	Measles (M)
Doses per person	1	3	1	4	5	1
Doses per vial	20	1	10	20	10	10
Packaged volume per dose	1.2	16.8	2.5	1	3	2.6
Packaged volumes per diluent	0.7	None	6	None	None	0.5
Route of administration	Intra-dermal	Intra-muscular	Sub-cutaneous	Intra-muscular	Intramuscular	Sub-cutaneous
Storage	Refrigerator	Refrigerator	Refrigerator	Freezer	Refrigerator	Refrigerator
Source	[65, 66]	[65, 66]	[65, 66]	[65, 66]	[65, 66]	[65, 66]

Table 5. Vaccine Supply Chain Cost Inputs

Variable	Value	Source
Supply Chain Human Resources		
Central-level personnel monthly salary ($US)	290 (range: 93-521)	[91]
Central-level personnel monthly benefits ($US)	57 (range: 9-149)	[91]
Central-level total number of personnel	26	[91]
Central-level personnel time devotion to EPI (percent per month)	1	[91]
Regional-level personnel monthly salary ($US)	300 (range: 94-521)	[91]
Regional-level personnel monthly benefits ($US)	43 (range: 9-93)	[91]
Regional-level total number of personnel	80	[91]
Regional-level personnel time devotion to EPI (percent per month	63% (range: 25-100%)	[91]
District-level personnel monthly salary ($US)	224 (range: 62-521)	[91]
District-level personnel monthly benefits ($US)	43 (range: 9-93)	[91]
District-level total number of personnel	420	[91]
District-level time devotion to EPI (percent per month)	63% (range: 25-100%)	[91]
IHC-level personnel monthly salary ($US)	148.9757914	[91]
IHC-level personnel monthly benefits ($US)	19	[91]
IHC-level total number of personnel	750	[91]
IHC-level time devotion to EPI (percent per month)	0.5	[91]
Supply Chain Transport Resources		
Cold truck replacement cost ($US)	74446	[91]
Cold truck fuel efficiency (L/100km)	25	[91]
Cold truck maintenance cost ($US)	93.0575	[91]
Total number of cold truck vehicles at baseline	2	Personal Communications
4x4 truck replacement cost ($US)	37383	[91]
4x4 truck fuel efficiency (L/100km)	20	[91]
4x4 truck maintenance cost per month ($US)	46.72875	[91]
Total number of 4x4 truck vehicles at baseline	42	Personal Communications
Motorbike replacement cost ($US)	5583	[91]
Motorbike fuel efficiency (L/100km)	7	[91]
Motorbike maintenance fee per month ($US)	6.97875	[91]
Total number of motorbike vehicles at baseline	695	Personal Communications

Table 5 (continued)

Supply Chain Storage Resources		
Cold room replacement cost ($US)	38600	[91]
Cold room maintenance cost per month ($US)	193	[91]
Cold room energy cost per month ($US)		[91]
Refrigerator replacement cost ($US)	1430	[91]
Refrigerator maintenance cost per month ($US)	168	[91]
Refrigerator energy cost per month ($US)	45	[91]
Freezer replacement cost ($US)	1433	[91]
Freezer maintenance cost per month ($US)	168	[91]
Freezer energy cost per month ($US)	45	[91]
Supply Chain Building Resources		
Cost of building (new construction) ($US)	97160 (range: 4717-225000)	[91]
Cost of building monthly fees (electricity, power, water, etc.) ($US)	405 (range: 20-938)	[91]
Supply Chain Utilities and Other Costs		
Storage and transport device useful life years	10	[91]
Storage and transport device annualization factor	8.53	[91]
Cost of fuel ($US/L)	1.1	[91]
Rate of inflation	0.03	[70, 91]

4.0 IMPACT OF INFLUENZA VACCINATION SEASON LENGTH AND TARGET POPULATION SIZE ON THE TRANG PROVINCE VACCINE SUPPLY CHAIN

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4.1 ABSTRACT

4.1.1 Background

Determine the potential vaccine distribution effects of introducing the seasonal influenza vaccine through the Trang province, Thailand, routine immunization program supply chain and the impacts of varying immunization campaign season lengths and target population sizes.

4.1.2 Methods

We constructed a computer simulation model of the Trang province vaccine supply chain that included all current National Immunization Program (NIP) vaccines, storage and transport devices from a subset of supply chain locations. To run the simulations, data were collected in collaboration with the Southern Thailand Vaccine Research Team (SVRT) and the Prince of Songhkla University (PSU) from the Ministry of Public Health (MOPH), the National Health Security Office (NHSO), and surveys and interviews conducted during site visits. We then simulated the introduction of seasonal influenza vaccine through the NIP supply chain along with other NIP vaccines while systematically varying the vaccination season length and target population size to determine the complex dynamic effects.

4.1.3 Results

As the influenza vaccine target population size increases (from 25-100%), introducing the influenza vaccine through existing storage and transport resources not only results in low vaccine

availability for the influenza vaccine, but also slightly impacts the vaccine availability of other NIP vaccines. Increasing the length of the influenza vaccination season (from 1 to 6 months) minimizes this impact. Trang province has ample storage capacity at all levels to accommodate the influenza vaccine in any of the evaluated scenarios. Transport capacity, however, was more constrained, particularly from the province-to-district level where for even a 25% target population size, transport capacity utilization increased from 31% (range: 21%-44%) at baseline to 71% (range: 28%-100%), 57% (range: 25%-100%), 48% (range: 24%-100%), 44% (range: 24%-100%), 41% (range: 23%-100%), and 40% (range: 23-92%) for 1-6 month campaign lengths, respectively.

4.1.4 Conclusion

Introducing the seasonal influenza vaccine into the Trang province vaccine supply chain, results in transportation bottlenecks between the provincial and district levels. These bottlenecks contribute to reductions in the availability of influenza vaccines and other routine vaccines for arriving patients. Increasing the length of the vaccination season can minimize this impact, however, with expected increases in future target coverage rates, reinforcements to the existing storage and transport resources may be required.

4.2 INTRODUCTION

Despite the ongoing significant public health burden of influenza, many countries lack efficient national plans and public health infrastructure (e.g., supply chain logistics) to distribute seasonal influenza vaccine[107, 108]. However, with increased interest in strengthening public health preparedness, many are now deciding to introduce the influenza vaccine into their immunization programs. As a result, these countries face important decisions regarding its distribution, including: (1) whether to distribute the influenza vaccine with other routine vaccines or in a separate supply chain, (2) which target groups to include in influenza vaccination programs, (3) which health facilities should administer the influenza vaccine, and (4) what would be the appropriate vaccination schedule and timeline. Following global recommendations on influenza vaccination by the World Health Organization (WHO), Thailand's government and other middle-income countries are now developing an influenza prevention program targeting individuals >65 years[109, 110]. In the coming years, the target groups will expand to include at risk groups <65 years, resulting in an increased number of doses required for procurement and distribution[110]. However, currently, little information guides the distribution of influenza vaccines in Thailand[110, 111].

While Thailand has a well developed public health infrastructure and one of the highest performing routine immunization programs in all of Southeast Asia, the influenza vaccine has historically been underutilized[112]. In previous years, fewer than 100,000 doses have been distributed through the private health sector among Thailand's population of over 65 million people, which is less than 1% of the total population[113]. The incidence of influenza in Thailand is between 18 to 111/100,000 persons annually, with the highest burden among children and the elderly, and has been shown to be a leading cause of pneumonia and febrile illness severe enough

to require hospital admission[111-113]. The costs associated with the burden of influenza in Thailand are estimated to be between $US23.4–$US62.9 million in economic losses annually, 56% of which are attributed to lost productivity, costs which are increasingly being used to inform national vaccine policy decisions[113]. Moreover, Thailand has reported four avian influenza pandemics since 2004[114]. Developing national immunization program capacities to include the seasonal influenza vaccine may not only improve vaccination coverage and health outcomes, but also allow Thailand to prepare for a potential future influenza pandemic during inter-pandemic years[115, 116].

Thailand's interest in introducing the influenza vaccine more widely, presented an opportunity to explore the impacts of implementing different distribution strategies for the seasonal influenza vaccine. Members of the Vaccine Modeling Initiative (VMI), a project funded by the Bill and Melinda Gates Foundation, collaborated with members of the Southern Vaccine Research Team (SVRT) from the Prince of Songkla University (PSU), located in Songkhla province, Thailand, to develop a computational model of the Trang province vaccine supply chain. We then employed this model to simulate the introduction of the influenza vaccine through the routine immunization program's supply chain in Trang province across varying influenza vaccination season lengths and target population sizes.

4.3 METHODS

4.3.1 Overview of Demographics in Trang province

In 2010, Thailand's population was 67,089,500 persons, of which 622,659 lived in Trang province; 19% in municipal areas and 81% in non-municipal areas[117, 118]. Trang province is 1 of 76 provinces in Thailand, located in southern Thailand, bordering the Andaman Sea, and has an area of approximately 5,000 square kilometers (2009 population density=133.3/sq.km)[117, 118]. The crude birth rate in 2008 was 14.7, and the crude death rate, 5.6 per 1,000 population[117, 118]. Infant mortality was 3.8 per 1000 live births[117, 118]. The gross provincial product (GPP) per capita in 2009 was 89,448 Thai Baht [2,961 United States dollars (exchange rate: 1 THB=0.0331USD)], the primary industrial components accounted for by agriculture, hunting, and forestry[118, 119].

4.3.2 Overview of Trang province Vaccine Supply Chain

Information used to model the vaccine supply chain in Trang province was collected in 2009. The current vaccine supply chain in Thailand is in a period of transition from a centralized five-tiered system to a three-tiered vendor-managed inventory system[1], but complete information on the vendor managed inventory system has yet to be collected. Until July 2010, vaccines passed through five levels to get from the manufacturer to the patient; the central, regional, provincial, district, and sub-district levels. Figure 1 shows the supply chain structure in Trang province. There are 149 supply chain nodes in Trang province including: 1 regional store, 1 provincial store, 21 district stores [including 3 municipal health centers (MHCs), 9 hospitals, and 9 district

health offices (DHOs)], and 126 sub-district stores. Data to construct the Trang province supply chain came from site visits at each level, surveys and interviews of nurses, pharmacists and managers at various locations, the Ministry of Public Health (MoPH), and the National Health Security Office (NHSO).

Vaccines supplied domestically are delivered to the central store or via the Government Pharmaceutical Organization (GPO), which repackages the vaccines before delivering them to the central store. Vaccines supplied internationally are delivered directly to the central store. The central store sorts vaccines into appropriately sized batches that are delivered to locations in 12 regions. Cold trucks from the regional level deliver vaccines every month to the Trang provincial store. District level sites use their own 4x4 trucks to collect vaccines from the province, monthly. Vaccines arriving at the district level are either administered (at the Hospitals and MHC's) or stored (at the Hospitals and DHOs) for further distribution. Sub-districts stores will then use their vaccine carriers to procure vaccines from storage sites at the district level once per month. All between-level shipments are staggered by one week to avoid vaccine stock-outs at the supplying level. For instance, shipments from the regional to provincial level occur in the first week of the month. Therefore, shipments from the provincial to district level cannot occur until the second week of the month, to ensure vaccines have arrived and are available at the provincial level.. The number of vaccines ordered by a vaccine administering site is governed by the previous month's vaccine demand at that site without ordering additional buffer stock.

Members of the VMI and SVRT research teams administered interviews with nurses, public healthcare workers and logisticians from the MoPH at various supply chain locations in Trang province collecting information regarding supply chain operating procedures, cold chain equipment and transportation inventory, and patterns of patient demand. Information from these

interviews indicated that approximately 60% of patients seek vaccination at district level stores, the majority of which administer vaccines once per week (range: 1 to 4 times per month). Remaining patients seek vaccination at sub-district stores, which administer vaccines once per month. The population demand at the district-level administering locations was estimated using the Trang province-specific population data from the '2000 Population and Housing Census' inflated by a 1.45% annual population growth rate to 2010[117]. Sixty percent of the estimated target population was allocated to each district proportionally to their population density, and the remaining 40% was evenly distributed to a given district's sub-district stores. Patients arriving at vaccination sites receive appropriate age-specified vaccines if the vaccines are available. Newborns receive vaccinations only at district level hospitals. A proportion of the population will seek vaccination through the private sector[120], however, we have assumed that enough vaccine is procured and distributed through the public sector vaccine supply chain described here, to vaccinate all children in Thailand.

4.3.3 Model Structure

HERMES (Highly Extensible Resource for Modeling Event-driven Simulations), a detailed, dynamic, stochastic, discrete-event simulation model was used to simulate the processes, locations, equipment and vaccines in the Trang province pre-vendor managed inventory supply chain. Development of HERMES was undertaken in Python programming language, using features from the SimPy package, and has been used to study various vaccine supply chain interventions in Niger and Thailand[121-123].

The model includes representations of the available refrigerator and freezer capacity at each location: the regional store has 34,660L of refrigerator and 272L of freezer space. The

provincial store has a total of 659L of refrigerator space (4 refrigerators with 165L each) and 410L of freezer space. DHO's have 750L of refrigerator and 13L of freezer capacity. District hospitals have 428L of refrigerator space and 197L of freezer space. MHC's have 171L of refrigerator space and 71L of freezer space, and sub-district health centers each have 140L of refrigerator and 25L of freezer space. Some of the refrigerator and freezer cold space in these devices is unavailable (i.e., consumed by shelving, ice trays, drawers, etc.), or is occupied by other temperature sensitive products (e.g., temperature-sensitive medicines or other biological vaccines). Therefore, our model evaluated scenarios in which 100% of total storage capacity was available, and scenarios in which only 85% of total storage capacity was available for NIP vaccines. Refrigerators are assumed to maintain a temperature of 2-8°C and freezers a temperature of -15°C to -25°C. Each vaccine's manufacturer-prescribed temperature profile governs its assignment to either a freezer or refrigerator.

Equation 1 illustrates how vaccine inventory (i.e., the number of vaccines currently stored in a refrigerator or freezer) is tracked in the model:

$$[\mathbf{1}]\ \boldsymbol{Vaccine\ Inventory\ for\ a\ Given\ Refrigerator\ or\ Freezer\ on\ Day}(\boldsymbol{t}) =$$
$$\big(Vaccine\ present\ on\ day(t-1)\big) + \big(Vaccines\ delivered\ on\ day\ (t)\big)$$
$$-\big(Vaccines\ shipped\ out\ on\ day\ (t)\big) - \big(Vaccines\ administered\ on\ day(t)\big)$$

Our model does not allow vaccine inventory to exceed a refrigerator, freezer or cold room's storage capacity. If vaccine inventory exceeds available capacity in HERMES, vaccines are stored at room temperature and expire at a faster rate. Vaccine shipments from location to location occur at pre-defined frequencies specific to the transportation route and should not

contain more vaccine vials than the transport vehicles' specified effective storage capacity. HERMES assumes that if vaccine shipment requirements exceed the available transport capacity, the excess vaccines (i.e., overfill) will not be distributed until the next shipment, and missed vaccination opportunities may occur. In reality, vaccines exceeding available shipping capacity may be delivered sooner than the next shipment (i.e., as soon as a vehicle is available for use). Transportation vehicles include a 4x4 truck (cold capacity: 9,187L) from the regional to provincial level, a cold box (cold capacity: 19L) from the district to the provincial level, and a vaccine carrier (cold capacity: 5L) carried by public health workers on motorbikes (majority) or by foot, by private car or by boat to their sub-districts.

Vaccine loss in HERMES occurs in three ways:

(1) Open vial loss occurs when vials are opened but not completely used (e.g., only one dose used from a five-dose vial)[5, 124].

(2) Inventory loss occurs when vials are broken due to mishandling or from excessively high or low temperature exposure during storage.

(3) Shipping loss occurs from similar incidents during transport. These forms of vaccine loss have been commonly reported in the literature[6, 92-94].

Our supply chain analysis considers the seven current NIP childhood vaccines administered in Thailand, and does not include school aged vaccinations (e.g., a second dose of the measles vaccine), which are administered at schools and not at district or sub-district locations, as they occasionally require the temporary mobilization of additional supply chain resources (e.g., additional cold boxes and refrigerators) beyond those used for NIP vaccines in school vaccination months during the summer. The characteristics of these vaccines are listed in Table 1 and were obtained from the WHO's Vaccine Volume Calculator and Prequalified

Vaccines Database[66, 67]. The model also accounted for the cold storage volume required by diluents needed to reconstitute certain vaccines, but only at administering levels. In previous years, the Thai NHSO has supplied the seasonal influenza vaccine in 4-dose vials, however, they are switching from a multi-dose vial to a single-dose vial. We have therefore used the single-dose vial for these analyses.

4.3.4 Introducing the Influenza Vaccine into the NIP

Our experiments involved introducing the influenza vaccine (packaged volume: 5.3cm^3/dose of vaccine, liquid formulation, 1 dose/vial) into the NIP through the vaccine supply chain managed by the MoPH along with the other NIP vaccines. However, unlike the routine childhood vaccines which are administered throughout the year and at both district and sub-district administering facilities, the influenza vaccine is typically administered within a short window from the vaccine's production cycle through the actual influenza season itself, and is only administered at the 9 district-level hospitals in Trang province.

Thailand is a sub-tropical country with monsoon rains occurring from May to October. The Thai MoPH has previously administered the southern hemisphere influenza vaccine in vaccination campaigns between April and May [112, 125, 126]. Each year, WHO Collaborating Centers review circulating strains of the southern hemisphere in September and decide which variants to include in the next season's influenza vaccine[127]. From that point, manufacturers have six months to produce a vaccine and distribute them to immunization programs[127]. Therefore, the earliest the influenza vaccine would be available for use in Thailand would be February of the following year.

While cases of influenza are reported throughout the year, Thailand typically experiences a peak in influenza incidence between the months of June and October, leaving three months from the anticipated time when vaccines are received to the time of peak incidence [116]. Moreover, it takes approximately 10 to 14 days for a person to develop immunity following seasonal influenza vaccination, though immunity only peaks after 4 to 6 weeks[128]. However, in previous years, peak activity has been reported as early as January to April [116]. This variability in peak incidence has also been observed in other sub-tropical countries, and makes it difficult to schedule annual vaccination campaigns [116].

4.3.5 Influenza Vaccination Campaign Season Length

Current influenza vaccines are manufactured through egg-based technology and require six months for development and release, which limits the number of months available for vaccine distribution and administration[114]. Moreover, the influenza vaccine is seasonal, and immunity against a particular strain is time-limited. As a result, annual vaccinations are required to maintain protection. We therefore simulated the introduction of the influenza vaccines over one year, systematically varying vaccination season lengths from 1 to 6 months.

4.3.6 Target Population Size

Influenza vaccines have not been widely used in Thailand, the majority of which have been distributed to the private sector including hotels and airline companies for their employees, and to the public sector including university hospitals and members of the MoPH[112]. Additionally, Thailand provides seasonal influenza vaccines to 30,000 Thai Muslims for their travel to Mecca

for the Hajj[112]. It is estimated that fewer than 80,000 doses of seasonal influenza vaccine have been distributed in Thailand in recent years, which would cover less than 1% of Thailand's 6.2 million inhabitants[112]. In 2009, 19,495 doses of the H1N1 influenza vaccine were supplied across Trang province to healthcare workers and patients with chronic conditions, which was enough to only vaccinate approximately 3% of the total population. To account for potential future supply chain requirements from the expansion of the influenza vaccination program to other target groups established by Thailand's Advisory Committee on Immunization Practice (ACIP), we also simulated the introduction of sufficient influenza vaccine doses to cover 25%, 50%, 75% and 100% of ACIP target groups in Trang province. These target groups for influenza vaccination include: (1) elderly >65 years, (2) pregnant women, (3) healthcare workers or people caring for elderly individuals, (4) people with chronic conditions <65 years, and (5) infants 6-23 months, as recommended by the WHO and the NHSO administrative guidelines for Thailand's influenza vaccine project in 2009, which account for approximately 11% of the total Trang Province population[109, 129, 130]. Each individual simulated receives one dose of the influenza vaccine. The vaccine selected for this analysis was the intramuscular influenza vaccine currently supplied in Thailand as a single-dose vial presentation, manufactured by Sanofi Pasteur.

4.3.7 Supply Chain Performance Metrics

Vaccine-specific vaccine availabilities were calculated for each vaccine administering location for each simulation (equation 2). The vaccine availability is the percent of patients arriving able to receive their desired vaccine because the vaccine is in-stock.

$$[2]\ \boldsymbol{Vaccine\ Availability} = \frac{\text{Number of patients receiving vaccine per immunization session}}{\text{Number of patients arriving at a clinic per immunization session}}$$

For example, if 20 children arrive at an IHC in a given session to receive the measles vaccine, but only 1 vial that contains 10 doses is available, only 10 children will receive vaccines resulting in a vaccine availability of 50%.

The model also tracked transport and storage capacity utilization (equations 3 and 4) at each location throughout each simulation, which can also be used to determine the amount of remaining available space, and quantify the frequency and magnitude of bottlenecks and stock-outs in the supply chain which can ultimately impact the availability of vaccines at administering locations.

$$[3]\ \boldsymbol{Transport\ capacity\ utilization} = \frac{\text{Total transport capacity consumed}}{\text{Total effective transport capacity available}}$$

$$[4]\ \boldsymbol{Storage\ capacity\ utilization} = \frac{\text{Total storage capacity consumed}}{\text{Total effective storage capacity available}}$$

4.3.8 Sensitivity Analyses

We systematically ranged the following parameters: shipping loss rate (range: 1-3%), inventory loss rate (range: 1-3%), and storage capacity utilization (85-100%). We also varied the population demand distribution between static, which means the number of patients arriving for

vaccination each month is fixed and does not fluctuate across months, and dynamic, which means the number of vaccine recipients in a given month draws from a Poisson distribution with a mean of (λ). A previously published study has systematically varied additional parameters to test for model robustness[121]. We validated HERMES by comparing simulation output with observations from the field in Thailand.

4.3.9 Computational Details

Each simulation was replicated and averaged over ten replications to determine the ability of the supply chain to handle the added volume of vaccines and increased population demand in shortened vaccination season lengths.

4.4 RESULTS

Sensitivity analyses demonstrated that varying the patient demand (static versus dynamic), shipping and inventory loss (1-2%), and storage capacity utilization (85-100%) did not notably affect the pattern of results, established using unpaired t-tests ($p>0.05$). However, the model was not robust to 3% shipping and inventory loss rates ($p<0.05$). The following results are therefore reported from scenarios representing 1% inventory and shipping loss, 85% capacity utilization, and dynamic monthly demand.

4.4.1 Overall Impacts

As the ACIP target population size increases from 25%-100%, introducing the influenza vaccine through the existing storage and transport resources in the routine NIP supply chain in Trang province results in reduced vaccine availabilities for the influenza vaccine, but also slightly impacts other vaccines supplied by the NIP during influenza vaccination campaign months. However, increasing the influenza vaccination campaign season length from 1 to 6 months minimizes this impact.

4.4.2 Impact on Transport

Figure 11 shows bar graphs of transport capacity utilization in each level's transportation device across varying influenza vaccination season lengths and target population sizes. Regional to provincial transport capacity was slightly impacted by the introduction of the influenza vaccine but never exceeded 8% of the available transport capacity. The average transport capacity utilization remained consistent across scenarios from the province to: (1) DHOs 20% (range: 9-37%), and (2) MHCs 15% (range: 12-20%).

However, the average transport capacity from the province to the hospitals across the 1 to 6 month scenarios was relatively more constrained and increased with increasing ACIP target population size from 31% (range across transport vehicles at this level: 21-44%) at baseline, wherein only NIP vaccines are distributed, to 49% (range: 22-344%), 69% (range: 22-652%), 89% (range: 22-960%) and 109% (range: 22-1268%) for target population sizes 25%, 50%, 75% and 100%, respectively. Transport capacity utilization above 100% indicates routes in which vehicle capacities are insufficient to transport entire shipment sizes. These result in portions of

vaccine requisitions being unmet and potentially, missed vaccination opportunities. Remaining vaccines were shipped the following month. Box plots in figure 12 show the variability in vaccine transport capacity utilization from the provincial to district level across evaluated scenarios.

Increasing the vaccination season length from 1 to 6 months reduced the transport capacity utilization and resulted in fewer routes between the province and district-level hospitals being overfilled. For example, introducing the influenza vaccine over longer campaign lengths reduced transport capacity utilization to an average across routes of 151% (range: 22-1268%) for a 1-month campaign to 90% (range: 22-655%), 70% (range: 22-450%), 59% (range: 22-347%), 53% (range: 22-286%) and 49% (range: 22-245%) for campaign season lengths of 2, 3, 4, 5, and 6 months, respectively.

4.4.3 Impact on Vaccine Storage

Figure 13 shows bar graphs of storage capacity utilization across varying influenza vaccination season lengths and target population sizes. The Trang province supply chain has ample storage capacity at all levels to accommodate the introduction of the influenza vaccine across the evaluated scenarios. Vaccine storage at the regional store, MHCs, DHOs and sub-districts never exceed 4% of the available space, and never exceed 6% at hospitals across all ACIP target population sizes and vaccination campaign lengths. Conversely, the provincial store is more space constrained, where storage capacity utilization increases across ACIP target population size, but decreases across vaccination campaign lengths from 14% at baseline to 33%, 50%, 67%, and 84% (1-month campaign length), 25%, 34%, 42% and 50% (2-month campaign length), 22%, 28%, 34% and 39% (3-month campaign length), 21%, 25%, 29% and 34% (4-

month campaign length), 20%, 23%, 27% and 30% (5-month campaign length), and 19%, 22%, 25% and 28% (6-month campaign length) for target population sizes 25%, 50%, 75% and 100%, respectively. Reducing the effective storage space from 100% to 85% further increases the space utilization in refrigerator devices and limits the remaining available space to store other temperature sensitive products.

4.4.4 Impact on Vaccine Availability

Transport bottlenecks ultimately have a substantial impact on vaccine availability at the service delivery levels. While the influenza vaccine availabilities increase with season length from 1 to 5 months, this effect is minimized as the size of the target population increases from 25% to 100% of the ACIP influenza target group. However, because other NIP vaccines are administered at all district and sub-district locations, the impact on their availability is minimal.

At baseline, the vaccine availability for the tuberculosis, diphtheria-tetanus-pertussis (DTP), oral polio, Japanese encephalitis, hepatitis-B (HepB), DTP-HepB, and measles vaccines are 95%, 95%, 97%, 94%, 94%, 96% and 95%, respectively. The initial vaccine availabilities are not 100% because in these scenarios, we assume 1% loss along each transport route and at each storage node. More importantly though, the ordering policy in Trang province proscribes ordering vaccines based on the previous month's demand which may not be a perfect representation of the next month's demand. Finally, open vial waste may result in wasted vaccines, which may reduce the availability of doses towards the end of a set of immunization sessions. Introducing the influenza vaccine across increasing vaccination campaign lengths decreased the vaccine availabilities of NIP vaccines slightly from 95% at baseline to an average

of 94% (range across ACIP target population sizes and influenza vaccination campaign lengths: 91-97%).

Conversely, the influenza vaccine availability increases as the vaccination campaign length increases. Figure 14 shows bar graphs of vaccine availabilities for the influenza vaccine across varying vaccination campaign season lengths and ACIP target population sizes. Introducing the influenza vaccine in a one-month campaign resulted in vaccine availabilities of 53%, 43%, 37% and 32% for ACIP target population sizes of 25%, 50%, 75% and 100%, respectively. Increasing the vaccination campaign length increased influenza vaccine availabilities to 69%, 54%, 49%, and 45% (2-month campaign length), 80%, 62%, 54%, and 49% (3-month campaign length), 89%, 68%, 59% and 54% (4-month campaign length), 96%, 74%, 64%, and 58% (5-month campaign length), and 96%, 80%, 68% and 62% (6-month campaign length) for ACIP target population sizes of 25%, 50%, 75% and 100%, respectively.

The reductions in the availability of the influenza vaccine were largely driven by five district hospitals which serve the largest ACIP target populations. The remaining four district hospitals did not experience vaccine shortages in any of the evaluated scenarios. Even in the 100% ACIP target group and 1-month vaccination campaign length scenario, providing additional transport capacity at the five districts that experience transportation bottlenecks improves the average NIP vaccine availability from 94% at baseline to 95%, and the vaccine availability of the influenza vaccine from 32% to 95%.

Considering the fact that patients who have never received influenza vaccination require two doses of the seasonal influenza vaccine, storage and transport capacities, and vaccine availabilities may be further strained.

4.5 DISCUSSION

Our results indicate that introducing the seasonal influenza vaccine through the routine immunization supply chain in Trang province, Thailand, not only affects the vaccine availability of the influenza vaccine, but also slightly impacts the availability of all other routine vaccines for arriving patients. Increasing the length of the influenza vaccine administration season improves the availability of the influenza vaccine, allowing more arriving patients to be vaccinated. However, longer vaccination campaign lengths and larger target population sizes can have negative impacts on other routine vaccines in the supply chain, and may also negatively impact the epidemiology of the spread of influenza.

The implications of our findings suggest that in order for the Trang province supply chain to accommodate the introduction of the seasonal influenza vaccine for their ACIP target groups, transport resources between the provincial and district levels may need to be augmented.

Alternatively, decision-makers may also consider integrating transport resources from parallel supply chains such as the private sector pharmaceutical chain. They may also consider expanding the season length of the influenza vaccination campaign, or if and where possible redistributing the demand for other NIP vaccines outside the influenza vaccination campaign months to lessen the stress on existing supply chain resources.

In order to ensure sufficient vaccine supply in seasonal and pandemic influenza scenarios, Thailand along with other countries other than North America and Europe are increasingly moving towards establishing local manufacturing processes for the influenza vaccine through the development of domestic human vaccine plants which will likely increase the availability of influenza vaccines in coming years[114]. A flexible supply chain and clear guidelines for the supply and distribution of the influenza vaccine domestically will be crucial to ensure optimal

vaccine availability while minimizing the wastage of vaccines and other resources. Determining appropriate target populations and identifying coverage goals for preparedness plans are equally important and should be done in tandem with evaluations of their impacts on existing vaccine supply chain resources. Regardless of the number of doses supplied to or in a country, if vaccines cannot reach their target populations through appropriate channels, they cannot be effective.

Moreover, the current lag between egg-based vaccine production and roll-out requires time for influenza strain identification and preparation, optimization of virus growth conditions, bulk manufacturing operations, quality control, and vaccine filling and release, limiting the season length to 6 or 7 months of the year[131]. With the potential adoption of cell-based vaccine production technology, public health decision-makers may be able to increase the length of the vaccination season, and thereby, minimize the impact of seasonal surges in vaccine requirements on the supply chain. While its production process is still in research, cell-based technology offers a faster vaccine production alternative to egg-based technology, allowing for more flexibility in the roll-out of the vaccine and scheduling of administration[132]. Therefore, considering the length of the vaccination season when developing seasonal influenza preparedness plans can help public health programs reach their target vaccine coverage rates.

On a wider scale, these findings are not only applicable to Thailand, but to other countries as well. Large-scale influenza surveillance and vaccination programs have historically been limited to wealthy countries. However, some middle-income countries are now better positioned to actively control influenza transmission by developing or expanding existing influenza immunization programs. These countries should conduct similar evaluations before considering introducing the new vaccine to ensure program and cost-effectiveness.

Our study highlights the utility of models in identifying effects of decisions not immediately evident. Models have long been used to help decision making in other industries, including meteorology [75], manufacturing [74], transportation [76], aerospace [77], and finance [78], and sports and rehabilitation [79]. Alternatively, their use to date in public health has not been as extensive [80-82]. Models have assisted responses to the spread of infectious disease such as the 2009 H1N1 influenza pandemic and health-care associated infections [83-87], however much of their potential remains untapped.

4.5.1 Limitations

By definition, all models are simplified representations of real life and therefore cannot capture every potential factor, event, or outcome. The model is based on data up to June 2010 and may not represent changes that may occur in the future. Actual demand may vary from our estimated demand, which was drawn from cross-sectional census data, although sensitivity analyses have demonstrated the effects of altering demand. Constructing our model involved substantial data collection from a wide variety of sources including records and interviews at different locations. As a result, parameter values may vary in accuracy and reliability, although sensitivity analyses demonstrated that model outcomes are robust under a wide variety of circumstances.

4.6 CONCLUSION

Introducing the seasonal influenza vaccine into the Trang province vaccine supply chain, results in transportation bottlenecks from the provincial to district levels. This bottleneck contributes to reductions in the availability of influenza vaccines and other routine vaccines for arriving patients. Increasing the length of the vaccination season can minimize this impact, however, with expected increases in future target coverage rates, reinforcements to the existing storage and transport resources will be required.

4.7 ACKNOWLEDGEMENTS

This study was supported by the Vaccine Modeling Initiative (VMI), funded by the Bill and Melinda Gates Foundation and the National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) grant 1U54GM088491-0109. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

We would like to acknowledge members of the SVRT: Ms. Chayanit Phetcharat, Mr. Somkit Phetchatree, Ms.Thunwarat Untrichan, Ms. Ratana Yamacharoen and Ms. Phornwarin Rianrungrot for their role in data acquisition.

4.8 FIGURES

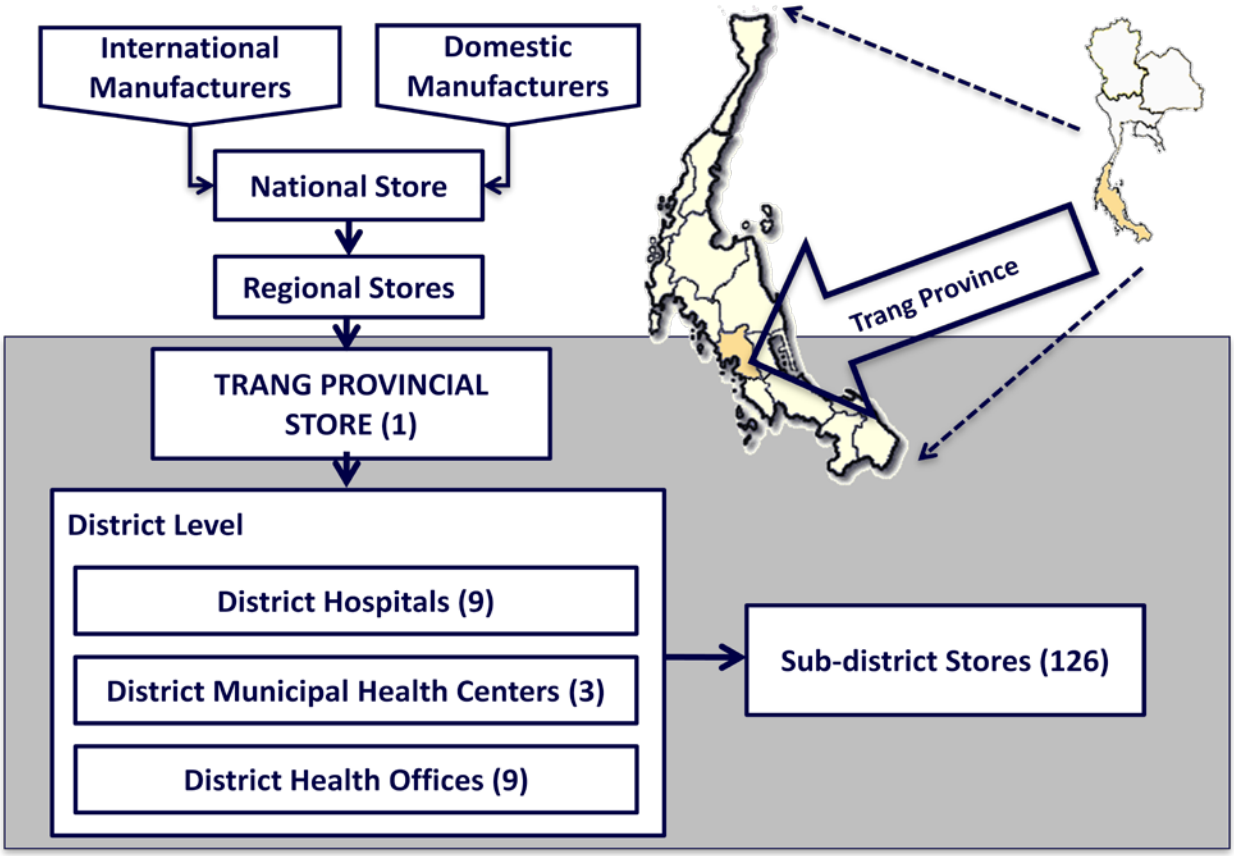

Figure 10. Trang province Vaccine Supply Chain Network

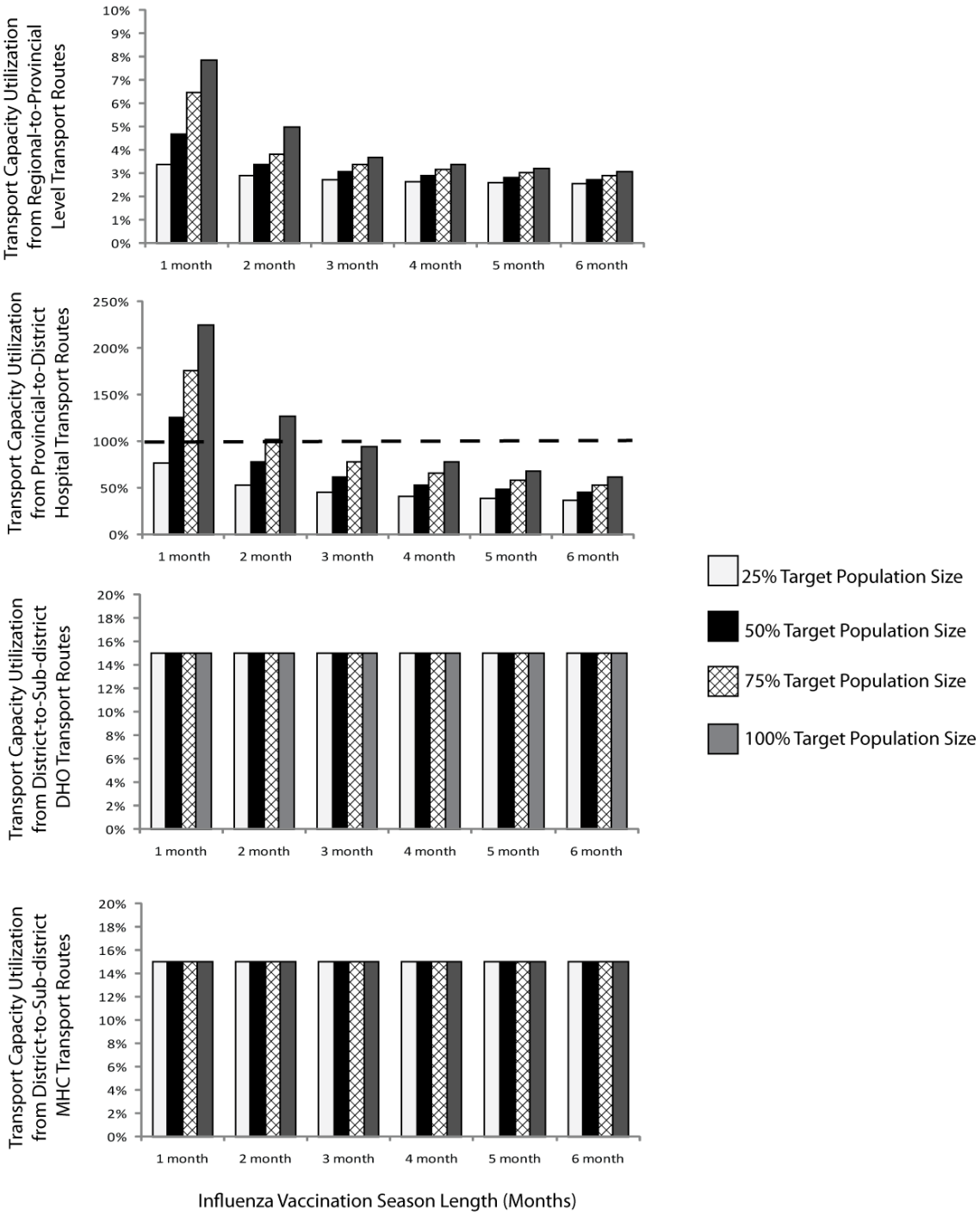

Figure 11. Average Transport Capacity Utilization by Level across Varying Influenza Vaccination Season Lengths and Target Population Sizes

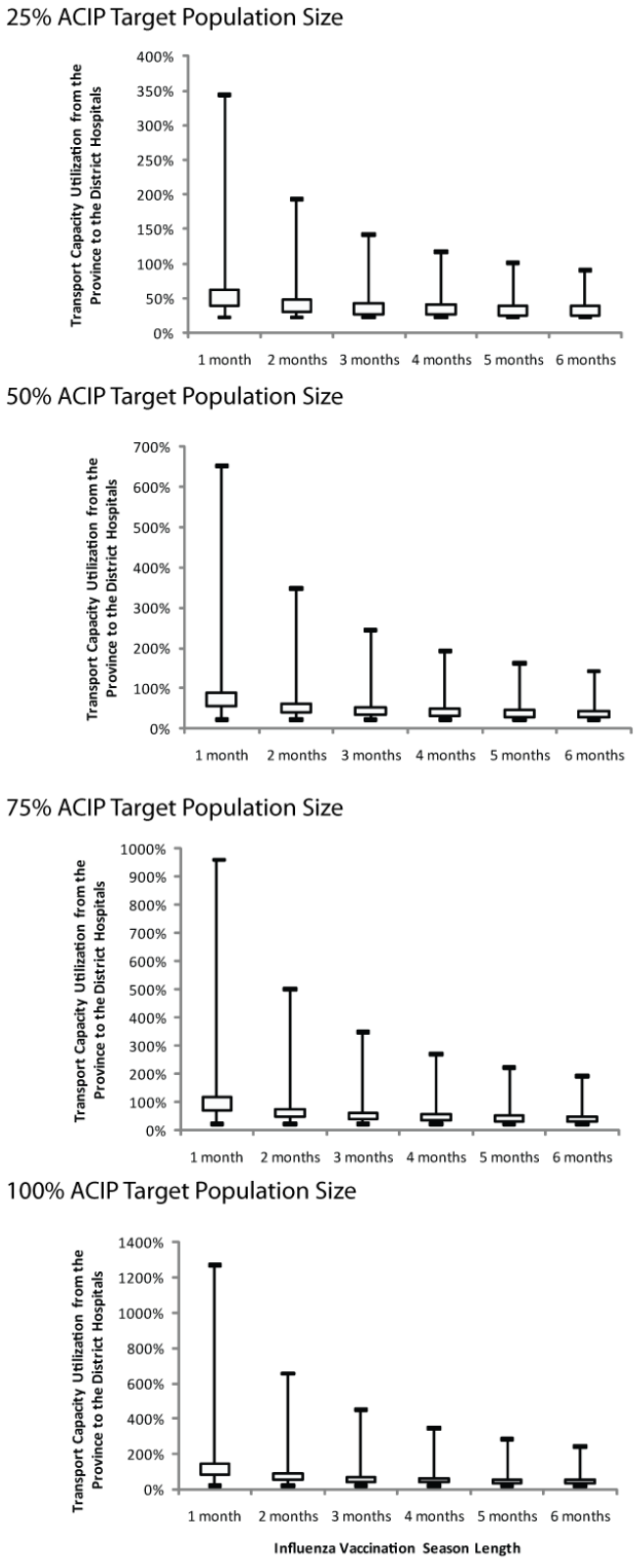

Figure 12. Box Plot of Transport Capacity Utilization Bottlenecks from the Provincial level to District Hospitals

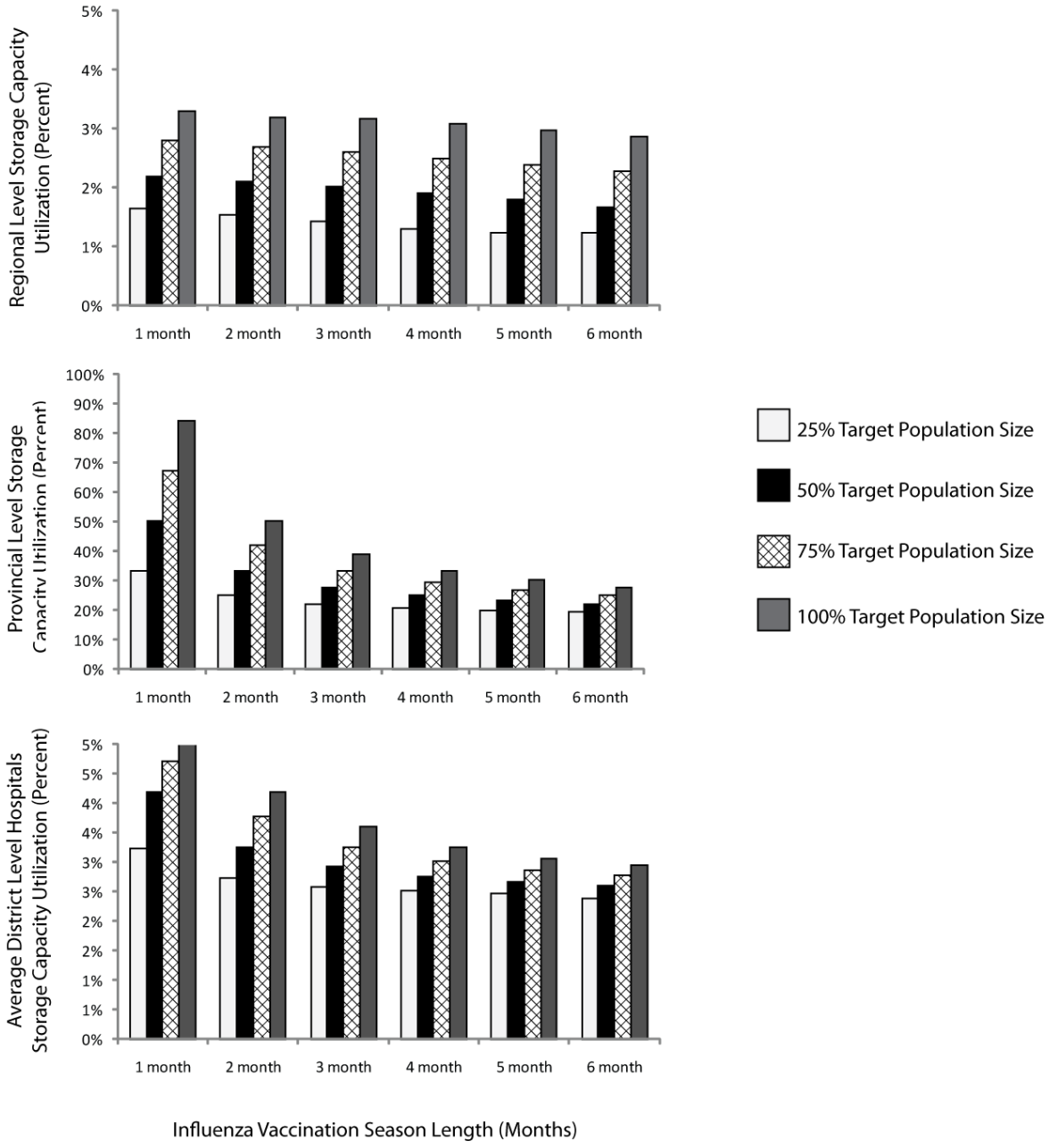

Figure 13. Average Storage Capacity Utilization by Level across Varying Influenza Vaccination Season Lengths and Target Population Sizes

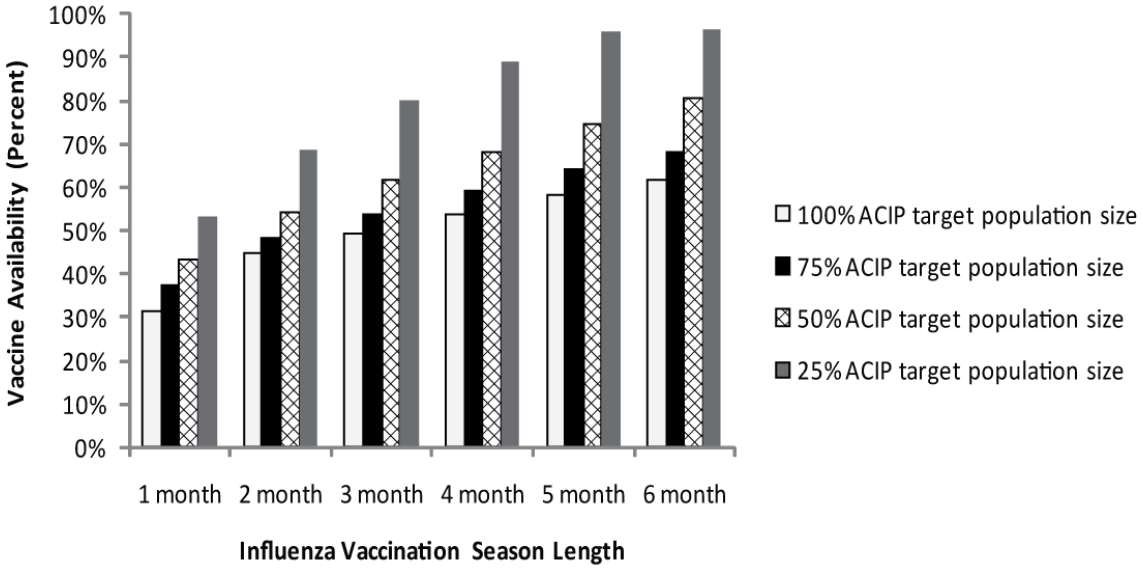

Figure 14. Average Influenza Vaccine Availability across Varying Vaccination Campaign Season Lengths and Target Population Sizes

4.9 TABLES

Table 6. Vaccine Characteristics in the Trang province Routine Immunization Program

Description (units)	Dose(s) /person	Packed volume/dose (cm^3)	Packed volume of diluent/dose (cm^3)	Storage preference	Target population	Source
Vaccine type						
BCG (10 doses/vial)	1	1.2	0.7	Refrigerator	Newborn	[51, 66]
HB (2 dose/vial)	2	0.5	-	Refrigerator	<1 year	[51, 66]
DTP (10 doses/vial)	5	3.0	-	Refrigerator	<5 years	[51, 66]
DTP-HB (10 doses/vial)	3	0.5	-	Refrigerator	<1 year	[51, 66]
OPV (20 doses/vial)	5	1.0	-	Freezer	<5 years	[51, 66]
M (10 doses/vial)	1	3.5	4.0	Refrigerator	<1 year	[51, 66]
JE (2 dose/vial)	3	0.5	11.5	Refrigerator	<3 years	[51, 66]
MMR (10 doses/vial)	1	0.5	0.5	Refrigerator	7 years	[51, 66]
dT (10 doses/vial)	2	0.5	-	Refrigerator	7, 12 years	[51, 66]
Seasonal Influenza (1 dose/vial)	1	5.3	-	Refrigerator	25%, 50%, 75%, and 100% of Trang province ACIP target groups	Personal Communi-cation*

**Packaged volume of seasonal influenza vaccine provided through personal Communications with members from the National Health Statistics Office in Thailand.*

5.0 SUMMARY AND DISCUSSION

Together, these works highlight the impacts that vaccine logistics can have on vaccine epidemiology. Changing a vaccine's vial size presentation can reduce the available space in transport and storage devices for other EPI vaccines and the resulting bottlenecks can lead to reductions in vaccine availability. Changing the structure of a vaccine supply chain by removing a level can improve transportation and storage efficiency but streamlining a supply chain is only effective if existing capital resources and shipping frequencies are considered and potentially modified. Finally, changing a national vaccine regimen by introducing a new vaccine for distribution through the EPI supply chain can cause considerable bottlenecks throughout a system, but knowing where these bottlenecks occur can help decision-makers better target new equipment procurement or equipment reallocation to ensure that the supply chain can accommodate these new vaccines without hindering the supply of other EPI vaccines. Making these changes to vaccine logistics systems without first evaluating their impacts on vaccine epidemiology could potentially have a considerable impact on infectious disease epidemiology.

6.0 PUBLIC HEALTH SIGNIFICANCE

Delivering vaccines to patients can be challenging, especially in a country like Niger that has limited public health infrastructure and resources to devote to its national immunization system. Niger's current routine immunization program under-performs in delivering vaccines to all women and children, with deficits in specific regions of the country. As a result, Niger faces persistent public health challenges such as recurring measles epidemics. Certain decisions regarding vaccine selection or the design of the vaccine supply chain network could improve vaccine availability at a greater proportion of locations in Niger, increase vaccine coverage and reduce disease transmission.

Alternatively, Thailand has a very high-performing routine immunization program. Rather than strengthening its routine immunization program, Thailand is in a position to expand its non-routine immunization and preparedness programs, including introducing new vaccines against seasonal influenza, rotavirus, and the pneumococcal conjugate vaccine. While the storage and transport resources available to the routine immunization program in Trang province are sufficient to accommodate routine vaccines, changes will need to be made in order to expand the country's vaccination services. Understanding the distribution of target populations and projecting the logistical resource requirements for vaccine distribution in a limited time frame can help determine where to provide new equipment or reallocate existing equipment, which can

help ensure programmatic feasibility of future vaccination campaigns and reduce disruptions to existing public health programs.

Vaccine preventable diseases cause considerable morbidity and mortality in several other LMIC's. Getting vaccines to women and children who need them could reduce this burden of disease. Strengthening vaccine supply chains is becoming increasingly important as the needs and sizes of target populations are growing. To accommodate these changes, interventions to immunization systems, programs and supply chains may need to be made. Managing and planning vaccine supply chain operations are complex tasks. Computational modeling can help formulate comprehensive representations of complex systems and evaluate wide ranges of interventions when field studies are impractical, and can help identify dynamic relationships and system-wide effects that may otherwise be unapparent. These computational evaluations of vaccine logistics and their impacts on vaccine epidemiology can aid decision-making processes and provide solutions of real public health significance. Findings from these evaluations are relevant not only to public health decisions makers, including ministers of health and vaccine logisticians, but also to vaccine manufacturers; vaccine procurement intermediaries including the WHO, UNICEF and GAVI, and international donor organizations.

7.0 FUTURE DIRECTIONS

A large proportion of Niger's population is rural. These marginalized communities often require immunization outreach services whereby public health workers transport vaccines to remote villages or other difficult-to-reach areas of the country beyond clinics at the lowest echelon of supply chains. This transport segment is separate from the ones modeled for this dissertation and is referred to as the last mile of vaccine distribution. The logistics of vaccine distribution in the last mile are particularly important as resources are more limited and the adverse environmental exposures to vaccines are typically more severe.

Additionally, the vaccine supply ratio, as computed in the works of this dissertation, indicates the availability of vaccines at the clinic level, but it does not indicate the number patients that actually arrive at the clinic and receive vaccination or those who accept vaccination during outreach services. Reasons for seeking or not seeking vaccination are complex and depend on numerous physical and behavioral contributors including religion, level of education, socio-economic status, and access to health services. Understanding and modeling the last mile challenges, whether logistical or behavioral, could help bridge the link between vaccine availability and vaccine coverage, and ultimately, infectious disease transmission. The relationship between vaccine availability and infectious disease transmission is geospatially dynamic. Modeling this relationship could illustrate how one impacts the other, where vaccines are most needed, and where logistics resources should be allocated to mitigate disease

transmission. An analysis of the last mile of vaccination will require an extension of data collection to behavioral determinants of vaccination and actual vaccination records.

Thailand's routine immunization program is in a state of transition wherein the current five-tiered decentralized system is being converted to a three-tiered vendor-managed inventory system. Ensuing changes to vaccine distribution routing networks and warehousing procedures will likely impact the manner in which vaccines are delivered to patients. Comparing the pre-vendor managed inventory system to the post-vendor managed inventory system could not only help inform Thai public health decision makers about these impacts of such changes, but also those of other countries considering similar transitions.

Through this dissertation and through other VMI projects, we have evaluated numerous vaccine supply chain interventions, including: new vaccine introduction, changes to vaccine presentations, changes to vaccine supply chain structures, and changes to national EPI regimens. Further utilizing HERMES to address other questions of interest to public health decision makers is an ongoing objective. Such questions include determining the impacts of integrating multiple parallel health commodity supply chains. This will involve collecting and incorporating new variables and data into the model that are currently not represented, including economic, vaccine coverage, and geographic information indicators. Extending our country-specific evaluations to other, more heterogeneous locations will also help generalize our findings to a wider range of countries and circumstances. Finally, the works of this dissertation suggest a link between vaccine logistics and vaccine epidemiology. The link between vaccine logistics and vaccine epidemiology, and infectious disease epidemiology remains to be learned. Determining the impacts of vaccine logistics on infectious disease transmission have on each other can help inform potentially important vaccine distribution decisions.

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