

Strategic Immunization Geo-temporal Mapping Application (SIGMA)

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Abstract:

The overall goal is to develop the Strategic Immunization Geo-temporal Mapping Application (SIGMA), a computational modelling tool to help decision makers: (1) forecast temporal demand for current and future adult immunizations, in a given country, in different parts of the country, and for each immunization location. (2) Determine the number and characteristics of adults that are reachable by current immunization locations and strategies in any given country. (3) Plan the locations and operating characteristics of various immunization strategies (e.g., outreach, campaigns, and other strategies) that are needed to supplement the fixed immunization locations. (4) Estimate the costs and cost-effectiveness of different adult immunization strategies from estimated demand scenarios. (5) Develop guidelines for adult vaccination use, to anticipate demand and to secure appropriate funding. (6) Demonstrate how robust these answers and solutions are to varying conditions (e.g., costs, population migration, mortality, and compliance with immunization). The key objectives of this project are to develop an initial version of SIGMA and utilize SIGMA for a pilot country (Mozambique) to evaluate the immunization logistics for a currently implemented adult vaccine (tetanus) and a planned adult vaccine (HPV). To evaluate the utility of SIGMA at the end of the project period, our team will convene a focus group of potential SIGMA users to evaluate and provide feedback on SIGMA. To quantify the increase in available information that SIGMA may provide, our team will catalogue what information is currently available on adult immunization logistics and then compare this to the information that SIGMA provides.

C. Main Section of the Proposal: Strategic Immunization Geo-temporal Mapping Application (SIGMA)

3. Overall Goal & Objectives

The overall goal is to develop the Strategic Immunization Geo-temporal Mapping Application (SIGMA), a computational modelling tool to help decision makers:

- a. Forecast temporal demand for current (e.g., in Mozambique, tetanus) and future (e.g., in Mozambique, HPV) adult immunizations, in a given country, in different parts of the country, and for each immunization location.
- b. Determine the number and characteristics of adults that are reachable and not reachable by current immunization locations and strategies in any given country.
- c. Plan the locations and operating characteristics of various immunization strategies (e.g., outreach, campaigns, and other hybrid strategies) that are needed to supplement the fixed immunization locations.
- d. Estimate the costs and cost-effectiveness of different adult immunization strategies from estimated demand scenarios.
- e. Develop guidelines for adult vaccination use, to anticipate demand and to secure appropriate funding.
- f. Demonstrate how robust these answers and solutions are to varying conditions (e.g., costs, population migration, mortality, and compliance with immunization).

SIGMA will be an innovative integrated software platform that combines geographical information systems (GIS) technology, logistics modelling, and economic and financing modelling to help key stakeholders evaluate and plan adult immunization. Such computational tools have transformed many other industries such as manufacturing, transportation, and meteorology. Such a tool would directly address the stated aims of the global request for proposal (RFP) from the International Society for Infectious Diseases and Pfizer Independent Grants for Learning & Change to model adult immunization rates and the costs associated with immunization rates in adults in low and middle income countries (LMICs), i.e., develop a logistics tool that can directly facilitate increasing adult access to or use of all relevant vaccinations at the individual and population levels, and evaluate and identify strategies to mitigate disparate care resulting from the geographic distribution of healthcare services.

SIGMA would also be very much aligned with the goals of the International Vaccine Access Center (IVAC), the Johns Hopkins Bloomberg School of Public Health (JHBSPH), and the Pittsburgh Supercomputing Center (PSC). IVAC's broad mission is to accelerate global access to life-saving vaccines through development and implementation of evidence-based policies. Led by the Principal Investigator of this proposal, the Operations Research Group at IVAC specializes in developing computational tools to further this mission. The JHBSPH is dedicated to education, training, research, and developing innovations that can improve health of populations around the world. SIGMA is also a natural extension of continuing multi-project collaboration with the Public Health Applications group at the PSC, which focuses on developing computational tools for public health decision-making.

The key objectives of this project are to develop an initial version of SIGMA and utilize SIGMA for a pilot country (Mozambique) to **(1) evaluate their current logistics of immunizing adults (i.e., cost, access, demand fulfilment, and vulnerabilities); (2) identify adult vaccination strategies to make the system more efficient, effective, and cost effective; (3) determine the return-on-investment (ROI) of these strategies (cost-effectiveness); and (4) estimate funding required to implement adult immunization strategies at defined price levels.**

The SIGMA project would be a natural extension of our extensive previous and ongoing work in global health operations/logistics and economics with strong experience in immunization.¹⁻

³⁶ Our team has considerable experience developing economics and logistics computational models and tools while working closely with partners such as country Ministries of Health (MOHs), UNICEF, the World Health Organization, GAVI, the Clinton Health Access Initiative, and a wide variety of in-country organizations such as Village Reach. For example, we have developed HERMES, a platform for modelling immunization supply chains, and utilized HERMES to generate simulation models of the childhood immunization supply chains for Niger, Senegal, Benin, Vietnam, Thailand, Kenya, and India.^{1,4,8,10,14,16,17,26,37-39} These have helped address questions such as what is the impact of introducing new vaccines or introducing new storage technology and how should supply chains be redesigned to improve the flow of vaccines to reach the population.

4. Technical Approach

a. Current Assessment of need in target area

A major continuing challenge in adult immunization, especially in LMICs, is finding ways to make vaccines readily available and convenient for adults. As our previous work has shown, even in high-income countries where resources are more plentiful, poor access is a major reason why adults do not receive the influenza vaccine each year.³³ In LMICs that have even greater constraints on resources, finding effective and cost-effective means to make vaccines more readily available for adults can be challenging. While studies have shown the substantial epidemiologic, clinical, and economics benefits of adult immunization in high-income countries (e.g., our economic modeling studies have demonstrated the cost-effectiveness of influenza vaccine from multiple perspectives in different scenarios), few studies have quantified these benefits in more limited resource settings.^{6,15,21,23,25,32,36,40-42} Many LMICs, such as Mozambique, have not even evaluated the logistics of their adult vaccine administration. Even fewer have used operations research (OR) analytics to evaluate the logistics of adult immunization and identify strategies to improve the logistics to increase adult immunization coverage.

Our initial pilot country, Mozambique, has all of these same needs for tetanus vaccine, a major adult immunization currently administered through the public system. **Currently, there is limited data forecasting the geo-temporal demand for tetanus vaccine and how well the logistics of tetanus administration currently matches and will match the population need.** Figure 1 shows considerable geospatial and temporal variability in tetanus coverage among pregnant women, ranging from 5% during the month of February 2012 in Maputo to 149% during the month of October 2012 in Niassa. The high variability suggests that the immunization logistics are not consistent across locations and over time. In recent years,

tetanus vaccine administration has fallen below the target rates due in part to the lack of reliable information matching population demand with supply, which causes increased stock outs and vaccine wastage at different locations. **SIGMA could provide much more granular and precise data on the matching and mismatching of adult immunization logistics and population needs.**

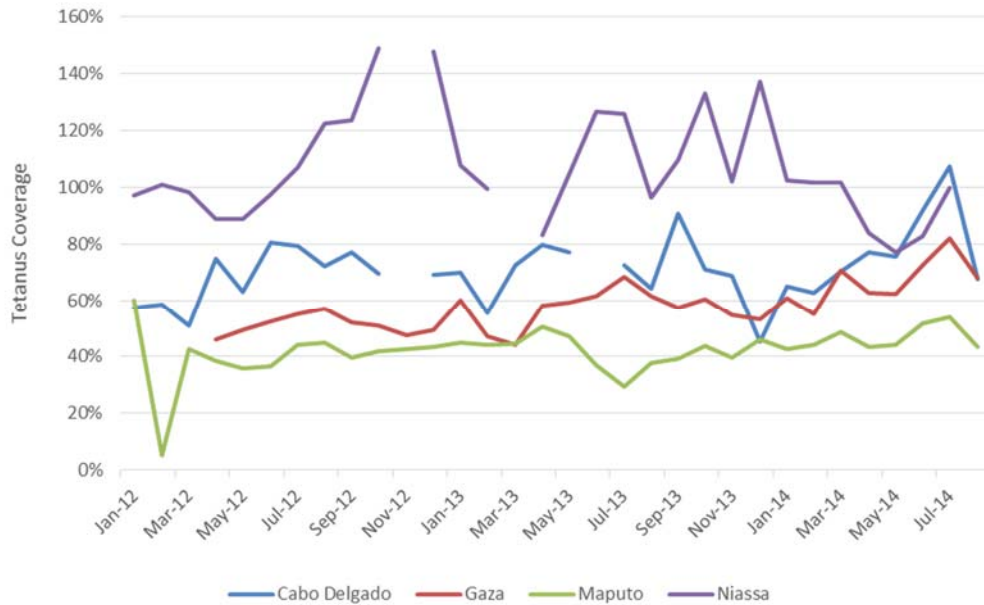


Figure 1: Tetanus coverage, pregnant women (2-5 doses), January 2012 to August 2014 in four provinces in Mozambique based on anticipated demand (coverage exceeds 100% when the number of immunizations for that month exceed anticipated demand).

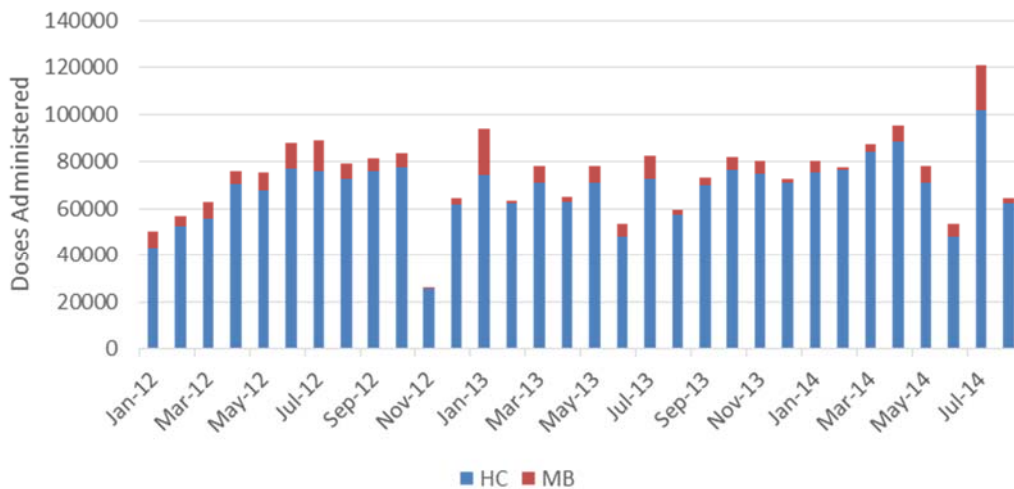


Figure 2: Tetanus doses administered in four provinces in Mozambique January 2012 to August 2014, at Health Clinics (HC) vs Mobile Units (MB).

As Figure 2 portrays, another key issue is that tetanus is administered through a combination of fixed health outposts and mobile units. **Currently, in Mozambique, there is no systematic method or tool used to determine the allocation of mobile units and fixed health outposts.** Most of these decisions are made with limited information or in an ad hoc manner. This approach has several risks. First, the current arrangement may miss portions of the population, leading to disparities in adult immunization. Second, vaccine wastage rates suggest that some

immunization locations may have more vaccines than the demand, leading to vaccine wastage, a major problem in countries like Mozambique that have limited resources.

Figure 3 shows the proportion of health facilities reporting tetanus vaccine stock-outs, which is further evidence that immunization logistics is not meeting demand for tetanus vaccine. A vaccine stock-out is when an immunization location runs out of vaccine to meet the demand. As Figure 3 demonstrates, **stock-outs of tetanus vaccine are occurring in all four provinces with the stock-out rate varying over the course of the year.**

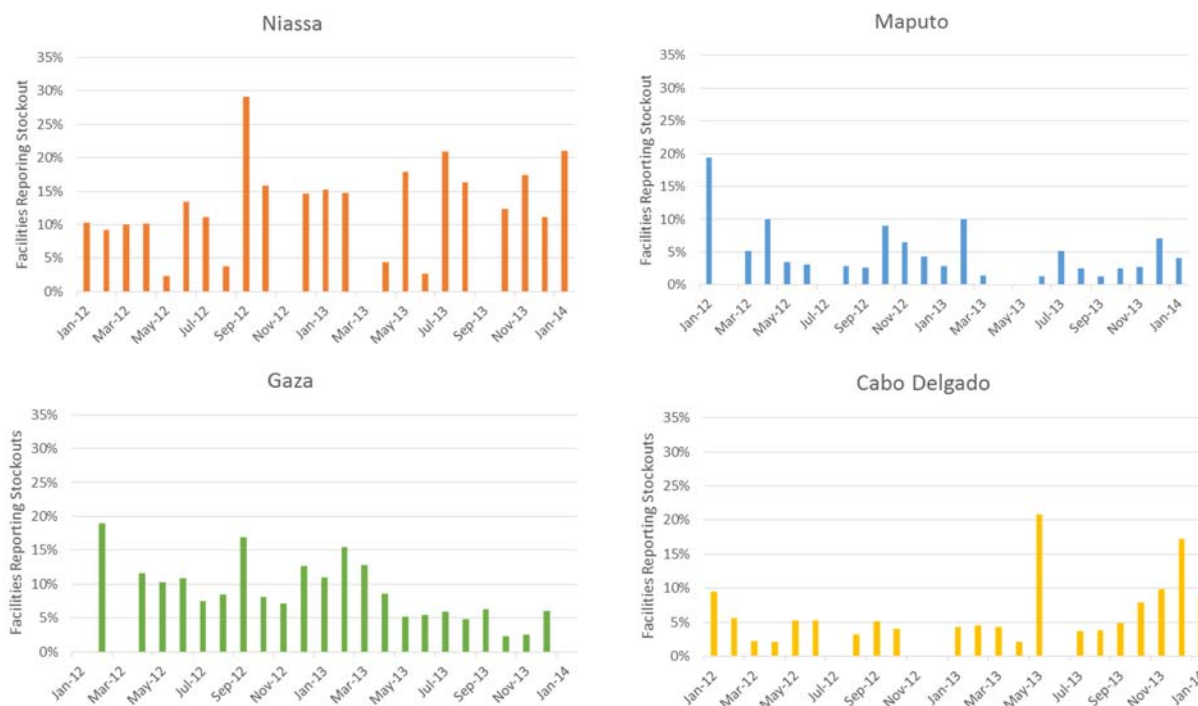


Figure 3: Proportion of Health Facilities in four provinces in Mozambique reporting tetanus vaccine stock-outs, January 2012 to August 2014.

An additional need will be guidance on the anticipated introduction of HPV vaccine to Mozambique, which may occur in late 2015. While the initial target for this introduction will be 9 to 13 years old girls, a large proportion of women who could benefit from HPV vaccine are older than this age group and in their adult years. Currently, the strategy and logistics of immunizing adult women has not yet been established. SIGMA could help decision makers in Mozambique evaluate, plan, and implement HPV immunization programs in this older age group.

b. Project design and methods:

For most LMICs, such as Mozambique, **SIGMA can fill the existing gap in computational geospatial analytic tools that can help stakeholders systematically evaluate and plan adult immunization logistics and, in turn, save the substantial cost, time, effort, and missed opportunities that would otherwise be spent with trial and error.** In addition, SIGMA could help country MOHs and other policy makers identify ways to increase adult access to vaccines and thus improve adult immunization rates and immunize adults in a more efficient, equitable

and cost-effective manner. SIGMA could also help funders target their efforts to improve adult immunization. Finally, SIGMA could assist manufacturers develop the appropriate technology to facilitate vaccine administration (e.g., appropriate vaccine containers, packaging, dosing regimens, and delivery, storage, and monitoring devices) to improve adult immunization. Most currently available GIS packages do not have the economic and logistics modelling and analytic features needed to properly and fully evaluate adult immunization programs. Moreover, existing GIS packages require extensive experience and expertise to use and the purchase of expensive software, which can be prohibitive barriers for LMICs.

Since this project aims to develop a new computational tool, its impact may reach well beyond the initial pilot country to many other LMICs. **By facilitating a new evidence-based approach to adult immunization planning and operations, SIGMA could impact many individuals and populations.**

c. Evaluation design

This project will be a success if it results in a functional version of SIGMA that can help improve the planning and operations of adult immunization systems in LMICs. Therefore, the first measure of the project will be whether a functional version of the SIGMA software platform exists at the end of the project period. Our team plans to make the SIGMA software platform available to all of those responsible for evaluating the success of this project along with a SIGMA training session if needed.

To evaluate the utility of SIGMA at the end of the project period, our team will convene a focus group of potential SIGMA users to try, evaluate, and provide feedback on SIGMA. The focus group will include a sample of **key stakeholders for adult immunization** such as representatives from in-country immunization programs, MOHs, manufacturers, funders, policy makers, and relevant non-governmental organizations. Our team will develop a questionnaire that will ask the focus group to rate SIGMA on its usability, applicability, feasibility and potential to improve decision-making. Our team also will interview the focus group members individually and in groups to offer an opportunity to provide more free-form critiques. We will assemble the information garnered from these questionnaires and interviews in a final report.

Several indicators can assess the impact of this project on the pilot country (Mozambique). First, the SIGMA software platform will be available to members of the Mozambique MOH and adult immunization program. The final workshop in Mozambique will consist of presenting results from our evaluation of the tetanus and HPV immunization logistics, training these representatives to use SIGMA, and asking them for feedback on the utility of both the results and SIGMA. This will involve questionnaires as well as individual and group interviews. This will include evaluating whether SIGMA provided information that can help identify the strengths, weaknesses, and potential improvements of the current adult tetanus immunization system and plan HPV immunization for adult women in the pilot country. This will include determining how well the current configuration of health outposts and mobile units matches the anticipated population demand for tetanus vaccine.

Since much of this information is currently not available to key stakeholders such as the MOH, SIGMA could provide more than a 50% increase (and potentially much, much more) in

information relevant to adult immunization planning and operations such as the forecasting of tetanus and HPV demand, the matching between the current logistics of tetanus and HPV vaccine administration and the population demand, and impact of changes in tetanus and HPV administration. To quantify the increase in available information that SIGMA may provide, our team will catalogue what information is currently available on adult immunization logistics and then compare this to the information that SIGMA provides.

Another measure of success will be the degree to which stakeholders are engaged throughout the project (i.e., what percentage of invited stakeholders participate in the workshops, show interest in the results, and indicate that they will make changes based on the study). Our team will keep track of who attends the workshops and take notes on what was discussed during the workshops.

Dissemination of the project results and outcomes would occur via five means: (1) direct presentations to key stakeholders (e.g., MOH, major policy makers such as the World Health Organization, major funders such as the Bill and Melinda Gates Foundation, key manufacturers, and the International Society for Infectious Diseases and Pfizer Independent Grants for Learning & Change); (2) presentation at scientific meetings (3) a manuscript ready to submit to peer-reviewed journals; and (4) making a functional version of SIGMA freely available via an unrestricted open source license to key stakeholders.

5. Detailed Workplan and Deliverables Schedule

For this project, our team will develop SIGMA for a pilot low-income country, Mozambique (where our team is currently developing computational tools to help the Mozambique MOH evaluate and improve their malaria control and EPI childhood immunization supply chain). Our team already is working in Mozambique for three different projects described below.

One project entails using our computational modelling software platform HERMES to evaluate and help improve the Mozambique childhood immunization vaccine supply chain. Funded by the Bill and Melinda Gates Foundation and UNICEF, this project is a partnership of UNICEF, Village Reach (see letter of support), the Mozambique MOH, and our team. Our team developed HERMES, which has been used to generate detailed discrete event simulation models of the childhood immunization supply chains in Niger, Benin, Senegal, Vietnam, Thailand, Kenya, India, and Mozambique. At the end of September 2014, our team and Village Reach will be holding a workshop at the Mozambique MOH to review HERMES results to date and teach MOH officials and immunization managers how to use HERMES.

A second project, funded by the Global Fund, involves utilizing our computational intervention portfolio evaluator JANUS to help the Mozambique MOH determine the impact of different combinations of malaria control interventions (such as insecticide treated nets and indoor residual spraying) in different locations. Our team held a workshop with the MOH in May 2014 and will be holding a follow-up workshop in October-November 2014.

The third current project in Mozambique, also funded by the Gates Foundation, is using computational modelling to evaluate the potential use of drones to transport vaccines from one location to another. Our team is simulating replacing motorcycles and other more traditional vehicles with these flying devices that can be operated remotely.

This ongoing work has given us experience working with the Mozambique MOH, clearly establish in-country partners, and generate preliminary data for our proposed SIGMA work. Included in this proposal is a letter of support from Village Reach, which has a longstanding presence in Mozambique, including an office in Maputo, and strong relationships with the MOH. They have access to the data needed to populate SIGMA and a strong interest in seeing its implementation.

Implementation of our project would occur over a two-year period. The project would proceed via the following seven Activities:

Activity 1: Work with the Mozambique MOH to determine the locations and logistics (e.g., setting, health care workers, procedures, and anticipated throughput/capacities) of these locations of immunizing adults with a vaccine currently implemented (tetanus) and vaccine that will be introduced (HPV). (Months 0-6)

This project will focus on **two vaccines**: one that is currently being implemented in Mozambique (tetanus) and one that will be introduced (HPV). First, our team will work with Village Reach to determine the locations of each fixed health outpost and mobile unit that deliver the tetanus vaccine. Figure 5 shows that we have already mapped the locations of health clinics in Gaza Province in Mozambique.

For each of the fixed health outpost, our team will determine what storage equipment, personnel, and assumptions about throughput and catchment area. For each mobile unit, we will determine the vehicles used, personnel, route/reach, and throughput.

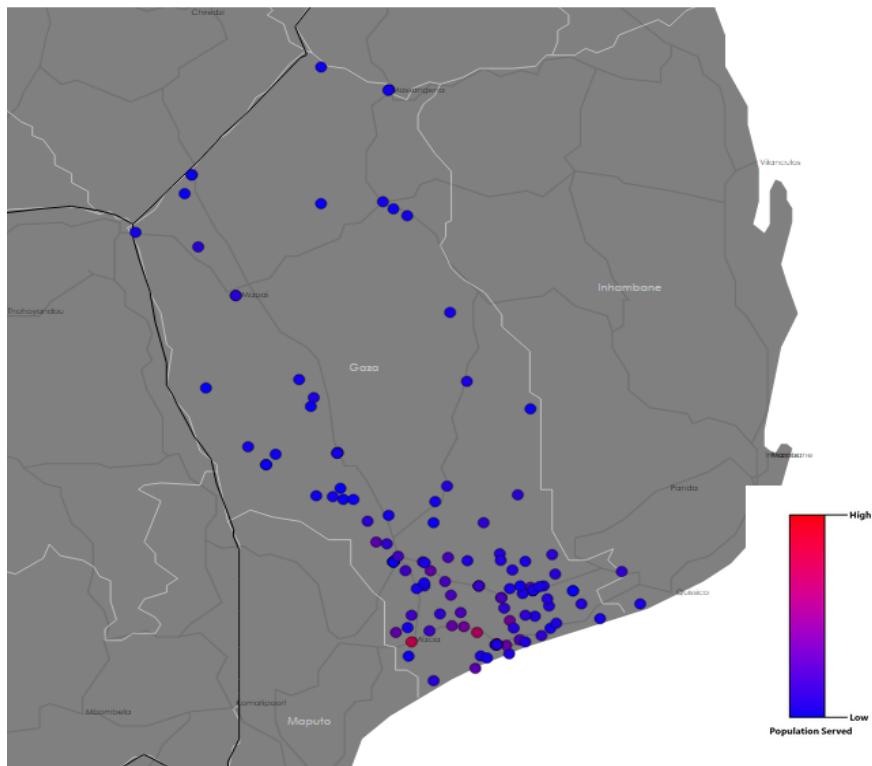


Figure 5: Previously mapped Health Facility locations in Gaza province. Each dot represents a fixed health outpost and the color of the dot represents the size of the population served (the more red the dot versus blue, the larger the population).

Activity 2: Estimate the costs associated with each step and component of adult immunization for tetanus and HPV (Months 0-6).

Next, our team will quantify the various cost components of tetanus and HPV adult immunization. The components fall into the following major categories: vaccine and vaccine accessory material (such as diluent and injection device) and vaccine program costs, storage costs, labor/personnel costs, building costs, and, for mobile units, the vehicle/travel costs. Vaccine and vaccine accessory material costs will come from the manufacturers. Average program cost per dose will serve as a proxy for incremental cost per dose. One source for these calculations can be the comprehensive multi-year plan (cMYP) data from the World Health Organization (WHO) and UNICEF¹. If no cMYP data is available for Mozambique or if data contains extreme values (<25% or >150% regional average), the formula below can tabulate this parameter.

$$\text{Cost}_{\text{Average/dose}} = ((\text{Cost}_{\text{RoutineRecurrent}} - \text{Cost}_{\text{Vaccine}}) + \text{Cost}_{\text{AnnualizedCapital}} + \text{Cost}_{\text{SharedPersonnel}}) / ((\text{Stock}_{\text{Beginning}} + \text{Quantity}_{\text{received}}) - \text{Stock}_{\text{Remaining}})$$

Alternatively, we can use the regional average. Storage costs will consist of amortization of the capital expenditures for the storage devices, energy costs, and maintenance costs. Our team already has these costs for most of the World Health Organization (WHO) pre-qualified refrigerators and freezers. Our amortization will be straight-line (i.e., linear) over the expected lifetime of the device (typically ten years). The labor/personnel cost will be the wage per unit time of the health care workers multiplied by the time spent on adult immunization. The time spent will be the time per vaccine administration times the number of vaccine administered. Vehicle costs will consist of amortization costs per kilometer, fuel costs per kilometer (from the vehicles fuel efficiency and the cost of fuel). Our amortization will be straight-line (i.e., linear) over the expected lifetime of the device in kilometres. Our team already has all of these costs for the majority of vehicles utilized in Mozambique for mobile immunization.

Activity 3: Map each of the adult immunization locations on a map of Mozambique, draw catchment areas for each location, and show how these relate to the population distribution. For example, this would show how the potential demand in a particular area matches the number of adult immunization locations and the potential throughput and the possible mismatches. (Months 0-6)

To map the expected population demand, our team will utilize the already available geospatial population distribution of Mozambique. This comes from the Global Rural-Urban Mapping Project (GRUMP), developed by the Socioeconomic Data and Applications Center. The dataset provides estimates of human population across the globe for the years of 1990, 1995, and 2000 in an approximately 1 km grid. The data set draws from a proportional allocation gridding algorithm that takes into account more than a million national and sub-national geographic units to assign actual population counts and then utilizes land area to develop population densities.^{43,44} The general birth rates and breakdown of the population by age strata can help transform the geospatial distribution of the population to a geo-temporal distribution of tetanus and HPV vaccine demand.

Overlaying the adult immunization locations and mobile units from Activity 1 on the population demand map will then allow us to compare how the available adult immunization channels may meet demand. This combined map will help determine the demand for each immunization location and the population not covered.

Activity 4: Evaluate the costs, effectiveness, return-on-investment, cost-effectiveness, and efficiency of current system. (Months 7-14)

Since Activity 2 will generate the operating costs for adult immunization, the other component needed will be estimates of the economic benefits of each tetanus and HPV vaccine administration. Two approaches will lead to these estimates, a cost-of-illness approach and an economic benefits approach. From an extensive review of the literature for epidemiological and economic data as well as data abstraction from economic databases, we will develop a model to calculate the incremental cost savings and DALYs averted from a tetanus vaccination and an HPV vaccination. The tetanus cost-of-illness considered will include the treatment and transportation costs associated with tetanus, caretaker wages lost as a result of an adult's illness with tetanus, productivity losses that occur due to premature death, and productivity losses that occur due to disability (particularly as a result of meningitis). Similar costs will be incorporated for the HPV expected cost-of-illness.

All model costs will be adjusted to most current year of analysis to maintain consistency with the base year of the model projection. This adjustment will be made by converting to local currency units at the baseline year of the study, adjusting for inflation using the same method as the World Bank consumer price index (CPI) series, and then converting to USD using World Bank exchange rates.⁴⁵

When Mozambique specific data is not available, we may extrapolate data from other similar countries, garnered from a literature review of all costing analyses related to tetanus and HPV. These studies will be grouped by WHO region and separated by GAVI eligibility (with preference given to studies conducted in the region of Africa or in GAVI eligible countries or). If only one study from the region of Africa is identified then this study will be used. If multiple studies fit the criteria for this process, then the selection will be made based on the geographical proximity of Mozambique or how closely the study adhered to the WHO guidelines for economic evaluations of vaccine programs.⁴⁶ If no acceptable studies are found, then the search will be expanded to include GAVI-eligible countries, under the assumption that costs would be comparable, and the same process will be used. In the event that costing data is not found for comparable conditions, then costing data from an adjacent WHO region will be incorporated.

To estimate DALYs averted from immunization, we will use standard methods and assumptions, including age-weighting, discounting and disability weights. The DALY parameters used are a discount rate (r) of 0.03, an age-weighting factor (K) of 0, an age-weighting factor (β) of .04, and an age-weighting constant (c) of 0.1658. Disability weights for the model outcomes (treated and untreated) will be derived from secondary data sources (2004 WHO GBD update⁴⁷), and will be based on proxy conditions (e.g. lower respiratory infection for pneumonia, meningococcal meningitis for meningitis, and meningococemia for NPNM IPD). Disability weights for sequelae

(e.g. treated and untreated sequelae) will also be based from secondary data sources (e.g. 1996 GBD study⁴⁸).

Systematic sensitivity analyses will explore the effects of varying key parameters to determine the robustness of our results and the effects of uncertainty and variability in our data.

Activity 5: Present our findings to stakeholders and work with them to identify strategies to test and evaluate the tool and improve the effectiveness and efficiency of the system. (Months 14-20)

Our team with the assistance of Village Reach will convene a progression of meetings/workshops in Maputo, Mozambique, with the MOH to review the plans and then results for the SIGMA Project: a planning meeting, followed by an interim interactive workshop, and then a final interactive workshop. These will be similar in format to the meetings and workshops that we have held for our other ongoing projects in Mozambique. Besides the MOH and immunization managers, invitees will include other stakeholders such as the World Health Organization (WHO) Afro office, clinicians, donors, and policy experts. The final workshop of this project will include presenting the results, discussing recommendations, training MOH personnel and immunization managers to use the initial beta version of SIGMA, garnering feedback to improve subsequent versions of SIGMA, and receiving advice on how to disseminate the results and SIGMA. As we have done in other countries such as Benin, one component of the workshops will be translating results to potential implementation of changes.

Activity 6: Wide dissemination of the results via direct presentations and a manuscript. (Months 18-24)

Since the SIGMA tool will not be specific to Mozambique but instead be subsequently applied to other LMICs, it will be important to disseminate SIGMA to stakeholders and countries throughout the world. One vehicle for this dissemination will be peer-reviewed scientific publications. For this project, our team will prepare and submit at least one manuscript describing SIGMA and its methodology and summarizing results from Mozambique.

Another vehicle will be presenting SIGMA to key international stakeholders such as the World Health Organization, GAVI, the Bill and Melinda Gates Foundation, the World Bank, and USAID. Our team has existing relationships with many of these organizations and have presented our other computational tools to them on numerous occasions. Our team will also identify a key immunization meeting to present SIGMA and the Mozambique results.

Activity 7: Develop our model into an initial software tool so that this process could be readily applied to other countries. (Months 0-24)

A key final product of this project will be an initial version of the SIGMA software tool, which will be web-based and developed in the Python programming language. Development of the SIGMA tool will proceed via the following Steps:

Step 1: Build the SIGMA Digital Library (Months 0-12)

An initial step will be to build a flexible digital library that can either hold data or link directly to existing open access databases to help readily populate SIGMA. One example is linking to the Natural Earth (<http://www.natureearthdata.com>), an open access database that contains

information on different country and administrative borders (e.g., states and districts). Another example is linking to the OpenStreets Project (<http://openstreetsproject.org/>), another open access database with detailed information about road networks and population centers, similar to what one can find on Google Maps. The SIGMA Digital Library also will link with the aforementioned Global Rural-Urban Mapping Project (GRUMP, <http://sedac.ciesin.columbia.edu/data/collection/grump-v1>) that has estimate of the counts of persons living within a certain resolution on the globe for a certain year (the resolution depends on the area of interest, but generally, approximately a 1 KM square).

The SIGMA Digital Library will also house relevant data that our team has already collected via our other ongoing projects. For instance, we have assembled an updatable database of existing vaccines and their various presentations, commonly used vehicles for outreach and mobile units, and commonly used storage devices (refrigerators, freezers, cold boxes, etc...) from the WHO PQS database (http://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/).

In addition to housing information and pulling from open access databases, the SIGMA Digital Library will also conduct calculations and processes that will combine and transform the available data into formats that can be usable by SIGMA (e.g., the SIGMA Digital Library will include data ingestion tools to automatically convert the Natural Earth data from the Shapefiles format, commonly used by GIS tools into a format readily usable for the modeling that SIGMA will perform). Additionally, since data may evolve over time (e.g., births, deaths, immigration, emigration, and migration may alter the population distribution), the SIGMA Digital Library will automatically update data as it changes in linked databases.

Since the data itself may be of interest to users, the SIGMA Digital Library will include a viewing and search function for users to browse the available data. The user may also want to upload relevant data that the user may have.

The SIGMA Digital Library also will allow the user to store the results of running different scenarios/experiments to retrieve later for comparison. For instance, the user may want to compare two different scenarios that configure adult immunization locations in different manners. The Digital Library can store the first scenario to be then retrieved to make comparisons with the second scenario.

Step 2: Construct the underlying SIGMA Immunization Demand Model (Months 6-12)

The next step will be to develop the model that will forecast the geo-temporal demand for adult immunization. This model will first draw the population distribution for the selected country or region and partition it on a uniform grid and then use the age distribution of the population to determine the geospatial distribution of different age strata. Next the model will project how the population distribution of different age strata may change over time. The difference between the number of births (calculated from the number of women of child-bearing age and the crude birth rates) and number of deaths (calculated from the mortality and the age distribution), modified by emigration and immigration rates if available, will govern how the population increases or decreases over time. Matching the geo-temporal distribution

of the different age/gender strata with the target ages and genders for a given vaccine will then generate the expected demand for that vaccine over space and time.

Step 3: Construct the SIGMA Immunization Location and Catchment Area Model (Months 6-12)

With the geo-temporal demand for each vaccine model in place, we then will develop the representation of the adult immunization locations. Each location will have a catchment area to define the population that it covers. The model will allow users to select among multiple options to define each location's catchment area. A simple approach would be to draw a circle around each immunization location and have the user input the distance of the radius for each circle. A more complicated is to delineate the catchment area by administrative borders (e.g., district or townships). Even more complicated will be incorporating road networks into defining the catchment area. In the absence of data, the "Voronoi polygons" approach can define the catchment area. An algorithm will assign population members to immunization locations that are closest to them. The SIGMA Model will be able to use all of these methods to define which of the grid cells are assigned to which immunization dispensary. This model will determine which members of the population are assigned to which locations and what segments of the population are not adequately covered by immunization locations.

Step 4: Construct the SIGMA Immunization Operations Model for each Immunization Location (Months 6-18)

Then our team will develop a model that for each immunization location will represent that location's storage and throughput capacity, key components and processes, and associated costs. So a given immunization location will have a user-defined frequency and maximum throughput rate (e.g., a health outpost may have an immunization session once a week and able to immunize one adult every 5 minutes; a mobile unit/outreach session may occur once a month and be able to immunize one adult every 10 minutes). The location's storage capacity and vaccine replenishment policy/frequency along with relevant characteristics of the vaccine (e.g., packaged size and doses per vial) will determine how many vaccines that location has available over time. This vaccine availability and the immunization session frequency and throughput rate will determine how many adults can be immunized over time.

Every process will have associated costs, described earlier under Activity 2. For example, each immunization session will have labor costs (i.e., equal to the duration of the immunization session multiplied by the wage per hour for the personnel) and vaccine and vaccine accessory material costs (i.e., the number of people vaccinated multiplied by the cost per vaccine dose and cost of the accessory materials needed). If the immunization session is conducted by a mobile unit then immunization session will have associated transport costs (i.e., the distance traveled multiplied by the per kilometer vehicle amortization, fuel, and maintenance costs). Storage costs will accrue over time.

Step 5: Construct the SIGMA Immunization Economic Model (Months 6-18)

The framework from Activity 4 will evolve into a model to determine the economic value of each successful immunization. Each immunization will result in cost savings and averted DALYs. For each scenario explored by SIGMA, SIGMA will calculate the overall costs savings and DALYs averted from the number of adults immunized and the incremental costs savings and DALYs

averted per immunization. The economic model will make various calculations such as the difference in costs, the incremental cost-effectiveness ratio, and the return-on-investment of changing the logistics of adult immunization. The Digital Library will enable such calculations. The user first can run and store in the Digital Library a scenario without the changes in the logistics of adult immunization and then run a second scenario with the changes. The SIGMA economic model can then compare the two scenarios, calculate the differences in costs (e.g., total costs, operational costs, and disease costs) and health effects (e.g., as measured in costs and/or DALYs) and make the following calculations:

Incremental cost-effectiveness ratio (ICER) = (Difference in costs between the two scenarios)/(Difference in health effects between the two scenarios)

Return on investment = (Difference in total costs between the two scenarios when health effects are converted into costs as well)/(Difference in operational costs between the two scenarios)

Step 6: Design the SIGMA Graphical User Interface (Months 10-24)

SIGMA will have an easy-to-use graphical user interface that will allow the user to enter data, build scenarios, perform model runs, and then view and visualize the relevant results. The GUI will operate through a standard internet browser (e.g., Internet Explorer, Firefox, or Chrome), either locally on a user's laptop, or remotely through the internet. Through the GUI, the user can select adult vaccines and immunization regimens of interest, choose a geographic area of interest (e.g., country, region, or province) and then place various fixed and mobile adult immunization locations/units in different places in this area. For each adult immunization location, the user can specify different relevant characteristics such as anticipated catchment area, cold storage available, personnel, and replenishment policies such as buffer stock, ordering thresholds and frequency as well as the relevant unit costs. For mobile units, the user can input key characteristics such as route/reach, vehicle types, fuel efficiency, and capacity, as well as relevant costs (e.g., capital expenditures, fuel costs, and maintenance costs).

After this information is inputted, the user will run the model through the GUI, which will then display the results in various tabular and graphic outputs. This will include cartographic representations (i.e., maps) of the population and immunization locations. Figure 6 shows an initial rough prototype of such a map that can be readily manipulated by the user.

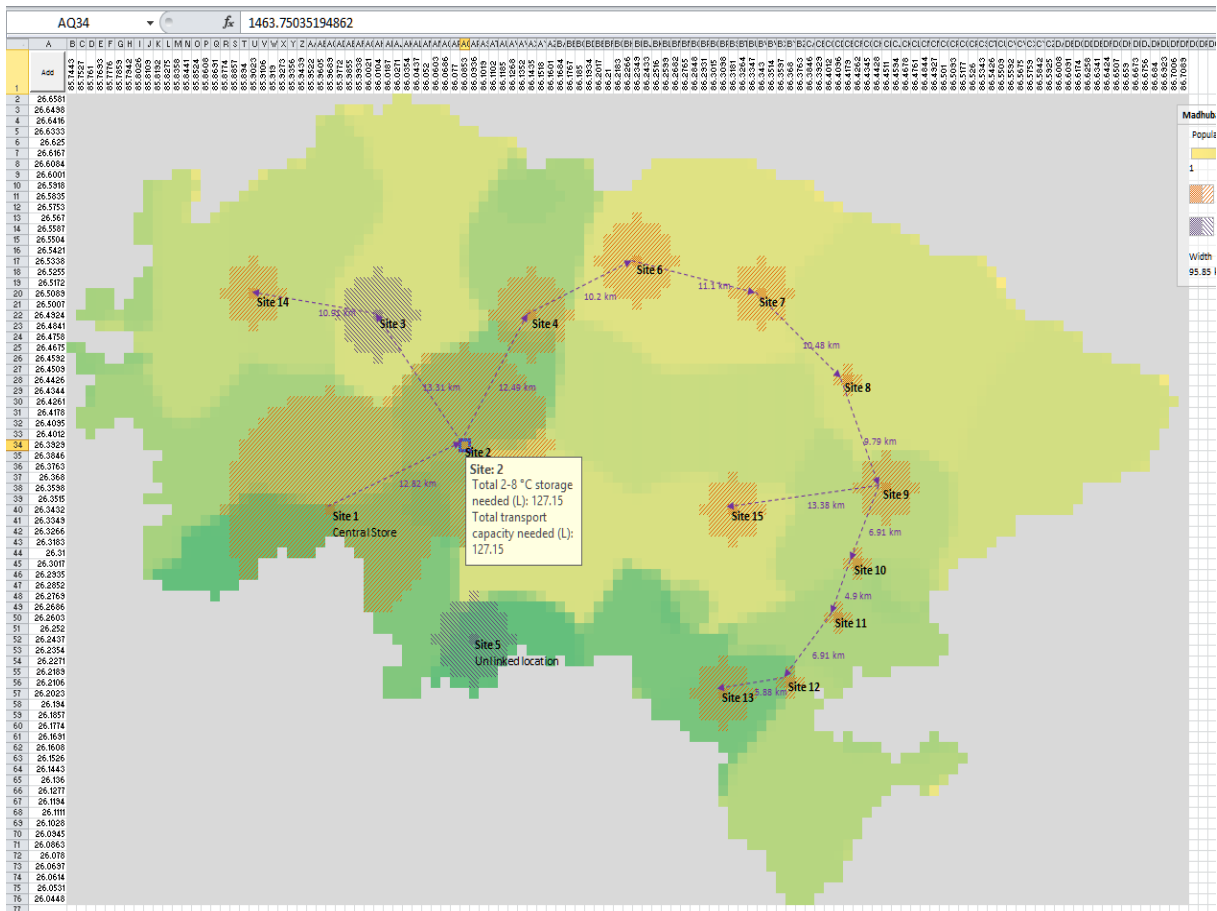


Figure 6: Screen shot of an initial prototype of SIGMA’s adult immunization mapping feature. This will be substantially enhanced for the SIGMA Project. The different shades in colors depict the population density with darker green representing increasing population density. Dots and names represent each immunization location. The orange area around each dot delineates that location’s catchment area.

Step 7: Develop documentation for SIGMA (Months 12-24)

This task will entail writing the initial draft of a concise basic SIGMA user’s manual, which will outline how to install and run the software, create and alter models, and conduct experiments as well as cover key features, and input/ output syntax. The GUI will incorporate relevant parts of this manual along with a search function. The documentation will also describe how to create and alter models and conduct experiments. The manual will be in clear and lay language.

Step 8: Beta release of SIGMA (Month 24)

Our team aims to make a version of SIGMA eventually freely available over the Internet via an unrestricted open source license. Our team will endeavour to have developed by the end of this project a fully functional beta version of SIGMA that can be made available to the Mozambique MOH, selected key stakeholders, and the International Society for Infectious Diseases. Feedback from these users may guide some refinement of SIGMA before an improved version is more widely released.

Activity 8: Evaluation of SIGMA and project. (Months 20-24)

As indicated earlier, to evaluate the utility of SIGMA at the end of the project period, our team will convene of focus group of potential SIGMA users to try, evaluate, and provide feedback on SIGMA. The focus group will include a sample of key stakeholders for adult immunization such as representatives from in-country immunization programs, MOHs, manufacturers, funders, policy makers, and relevant non-governmental organizations. Our team will develop a questionnaire that will ask the focus group to rate SIGMA on its usability, applicability, and potential to improve decision-making. Our team also will interview the focus group members individually and in groups to offer an opportunity to provide more free-form critiques. We will assemble the information garnered from these questionnaires and interviews in a final report.

An estimated timeline for each proposed deliverables and associated cost of each is presented in Table 1. This timeline may be revised at a later time to ensure that key deliverables are sequenced with important milestones of this project.

The total budget for this project is US\$292,873. Personnel travel and supplies have been justified in Appendix 1.

Table 1: Summary of deliverables schedule

Deliverable	Due	Budget
Report evaluating Mozambique current tetanus and planned HPV adult immunization logistics and how these match with anticipated demand	By Month 12	\$29,287
Initial workshop in Mozambique	By Month 12	\$11,715
Final workshop in Mozambique	By Month 24	\$14,644
Initial version of SIGMA Software Platform	By Month 24	\$161,080
SIGMA Users' Manual	By Month 24	\$17,572
Manuscript describing SIGMA and final Mozambique results	By Month 24	\$43,931
Report summarizing stakeholder feedback on SIGMA	By Month 24	\$14,644
TOTAL		\$292,873

D. Organizational Detail

1. Leadership and Organizational Capability

The Principal Investigator (PI) of the SIGMA Project will be Bruce Y. Lee, MD, MBA, Director of Operation Research at the International Vaccine Access Center (IVAC) and Associate Professor of International Health at the Johns Hopkins Bloomberg School of Public Health (JHSPH). Dr. Lee will oversee the development and implementation of the SIGMA software platform. The Co-PI will be Dagna Constenla, PhD, Director of Economics and Finance at IVAC and JHSPH. Dr. Constenla will oversee developing the economic model and analyses for the SIGMA Project.

The International Vaccine Access Center (IVAC) aims to accelerate global access to health measures through development and implementation of evidence-based policies. Dr. Lee's Operations Research team focuses on developing various mathematical and computational models and tools to improve the means by which health care services and products are developed, delivered, and administered throughout the world. Dr. Constenla's Economics and Finance team takes an integrated and collaborative approach to analyse the economics and finance of public health technologies, address disparities found in immunization programs and demonstrate the economic value of new and underutilized vaccines.

IVAC occupies approximately 10,000 square feet of office space in the John G. Rangos Building which is L.E.E.D. Certified. IVAC's internationally renowned experts research areas focus on epidemiology, economics and finance, policy, advocacy, communications and operations research. The Center has seven directors, 11 faculty members, 15 research associates and statistical analysts, seven project and administrative analysts and 47 graduate students for the 2012-2013 academic school year. The facilities include eight offices, five semi-private workstations, 22 small workstations, four small and medium conference rooms, two large conference rooms with video conferencing capabilities and two SMART® Boards for presentations. All rooms have PolyCom® conference calling capabilities for domestic and international calling. Each faculty member has an office including state of the art computing (EnergyStar® rated), internet (Ethernet and Wi-Fi) and e-mail programs as well as office and data analysis software as needed. All offices are situated to provide efficient communication equipped with desks, computers, telephones, printers, and a shared fax machine.

Both Dr. Lee and Dr. Constenla are full-time faculty members in the Department of International Health, the largest of JHSPH's 10 academic departments with 148 full-time faculty members and a research portfolio extending to almost 90 countries. Its mission is to understand health problems and develop means of disease reduction and health protection and promotion among underserved populations around the globe. International Health draws on all public health disciplines for application in global settings and emphasizes masters and doctoral training programs for students with international and cross-cultural interests. The Department is organized into four program areas: Global Disease Epidemiology and Control, Health Systems, Human Nutrition, and Social and Behavioral Interventions.

The Johns Hopkins Bloomberg School of Public Health (JHSPH) is a leading global health institution with nearly a century's history of excellence in research, training, and public health practice. The JHSPH has ongoing research projects in the United States and more than 90 other

countries. It is the largest school of public health in the world and is consistently ranked first among public health schools in the US by *U.S. News & World Report*. It has 529 full-time and 623 part-time faculties devoted to work in public health. JHSPH performs millions of dollars in research and technical support activities every year and has the necessary equipment and facilities to meet the demands of this project.

A long-time close collaborator of Dr. Lee's, the Pittsburgh Supercomputing Center (PSC) will provide computational and software development support for the SIGMA Project. For 27 years, the PSC has provided university, government, and industrial researchers with access to several of the most powerful systems for high-performance computing, communications and data-handling available to scientists and engineers nationwide for unclassified research. PSC advances the state-of-the-art in high-performance computing, communications and informatics and offers a flexible environment for solving the largest and most challenging problems in computational science. The center is a joint effort between Carnegie Mellon University, the University of Pittsburgh and the Westinghouse Electric Company. Established in 1986, PSC is supported by several federal agencies including the NSF, NIH, DOE, DOD, BMGF, the Commonwealth of Pennsylvania. The Public Health Applications (PHA) group at the PSC was formed in 2012 with the mission of developing novel computational infrastructures, platforms, models, and tools to empower public health decision making. Led by Dr. Shawn T. Brown, the team includes members with a wide-range of expertise and experience in public health, in software development, and in working closely with decision-makers around the world. PHA employs several programmers to develop software infrastructure and platforms for public health simulation, decision support, and data analytics. The group has developed software for immunization supply chain logistics (HERMES); economic, operations and health systems modeling (JANUS); common frameworks for modeling infectious disease spread (Apollo) and many other projects over several aspects of public health. Software developed by the group has been deployed in several countries including Benin, India, Senegal, Mozambique, Niger, Vietnam, Thailand, Kenya, and the United States. A staff developer from PHA will be assigned to this project, and managed by the IVAC team to develop SIGMA (please see Letter of Commitment).

Village Reach (please see Letter of Commitment) will serve as our SIGMA's team in country partner. They will facilitate data collection for the Project and interactions with the Mozambique MOH. Our Johns Hopkins team has already been working closely with Village Reach on the HERMES Project in Mozambique funded by the Bill Melinda Gates Foundation and UNICEF. VillageReach is an international non-governmental organization (NGO) headquartered in Seattle, WA with field offices located in Malawi and Mozambique, Africa. Through collaboration with public and private sector partners, VillageReach seeks to increase access to quality healthcare for the world's most underserved communities, bringing life-saving innovations to scale and sustainability. VillageReach develops, tests and implements innovations that uniquely address barriers at the lower levels or "last mile" of healthcare delivery in low-resource communities including medicine availability, human resource constraints, data visibility and lack of infrastructure. Effective solutions require a deep understanding of local health systems, a diverse set of skills and expertise, and strong relationships on the ground in order to achieve sustainable impact. Our experience -- over a

decade of studying and working in low-resource communities in sub-Saharan Africa and around the globe -- has greatly influenced our focus on the areas that have the greatest potential for large-scale impact to save lives and improve health outcomes.

VillageReach has been working with the Mozambique Ministry of Health since 2001 to improve vaccine coverage rates. VillageReach currently works in partnership with the provincial governments of Maputo, Cabo Delgado, Niassa, Nampula, Gaza, and Tete provinces to support immunization system design and implementation.

2. Staff Capacity

Bruce Y. Lee, MD MBA (PI with 10% effort on the SIGMA Project; Country of Residence: USA) is committed to the development and implementation of SIGMA and will lead the overall development and application of SIGMA. SIGMA is fully in line with Dr. Lee's longstanding interests, expertise, and history of developing software platforms for public health and medical decision making. Dr. Lee has over 15 years of experience leading similar team project in both industry and academia. His previous positions include serving as an Associate Professor at the University of Pittsburgh, Senior Manager at Quintiles Transnational where he led teams that developed economic and operational models for a variety of clients in the pharmaceutical and medical device industries, working in biotechnology equity research at Montgomery Securities, and co-founding Integrigen, a biotechnology/ bioinformatics company. His research group, Public Health Computational and Operations Research (PHICOR), focuses on public health operations research, developing and utilizing mathematical and computational methods and tools to better understand and assist public health decision-making, processes, and systems. A member of Dr. Lee's research team will help develop SIGMA along with a programmer from the PSC.

Dagna Constenla, PhD (co-PI with 10% effort on the SIGMA Project; Country of Residence: USA) longstanding interests and experience in international vaccine economic analyses and models make her the right person to lead the SIGMA economic model development and analyses. Of note is her extensive experience in applying mixed methods research, health economics and finance methods in low and middle-income countries. Dr. Constenla has led research programs to evaluate vaccines in various low and middle-income countries. She has spent much of her career generating new evidence to support government decision-making at the local and regional levels. Dr. Constenla will be responsible for the overall progress of the economic component of the project, for engaging the team as well as local experts in the setting of the project's strategy, and carrying out some of the modeling and analyses. Dr. Constenla is well placed for this position and has experience successfully leading team projects of this nature.

Two research associates, (TBD) (15% effort each on the SIGMA Project; Country of Residence: USA), with a background in health economics and health systems at JHU's IVAC and the University of Pittsburgh will be engaged in various aspects of the project assisting with the literature review and with the development of SIGMA, data collection and data analysis.

Our SIGMA team has been and will continue to interact closely with the Village Reach team members including all of those based in Maputo, Mozambique.



Bruce Y. Lee, MD MBA
Associate Professor of International Health
Director of Operations Research, International Vaccine Access Center (IVAC)
Johns Hopkins Bloomberg School of Public Health
855 N. Wolfe Street, Suite 600
Baltimore, MD 21205

September 19, 2014

Dear Dr. Lee:

VillageReach is delighted about the possibility of expanding our existing collaboration with your International Vaccine Access Center (IVAC), Johns Hopkins School of Public Health, and Pittsburgh Supercomputing Center team in Mozambique via the SIGMA Project. As you know, we already have been working closely with your team on the HERMES modeling of Mozambique's childhood immunization supply chain and helping the Ministry of Health (MOH) of Mozambique to evaluate and improve childhood vaccine delivery. We are looking forward to the joint workshop with your team and ours at the end of this month, and with the Mozambique MOH to review the HERMES results to date, build capacity of a local team, and demonstrate how to use the HERMES tool, a software platform that can generate a detailed simulation model of any vaccine supply chain. VillageReach has been working in Mozambique for many years and has a deep network of connections that can facilitate the SIGMA project.

The SIGMA Project would be very much in line with our interests and expertise. Founded in 2000, VillageReach is a nonprofit 501(c) (3) organization focused on infrastructure and logistics in low-resource settings. VillageReach improves access to healthcare around the world. We partner with governments, businesses, and other organizations to improve the performance and reliability of health systems in the most inaccessible and isolated last mile communities. VillageReach has a field office in Maputo, Mozambique.

SIGMA has tremendous potential not only in Mozambique but also in many other countries. In Mozambique, better understanding and improving adult immunization would be of strong interest. We have helped identify specific immunizations (tetanus and human papilloma virus) that would be of immediate interest. Using SIGMA would help better plan and bring efficiencies to adult immunization. As you know, the data to populate SIGMA (e.g., locations and logistics of both fixed health outposts and mobile units as well as the current and planned adult immunization programs) are available. We would be happy to work with your team and the MOH to obtain this data to populate SIGMA.



VillageReach very much looks forward to this possible project. If you have any further questions, please do not hesitate to ask.

Sincerely,

A handwritten signature in black ink that reads "Emily Bancroft". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

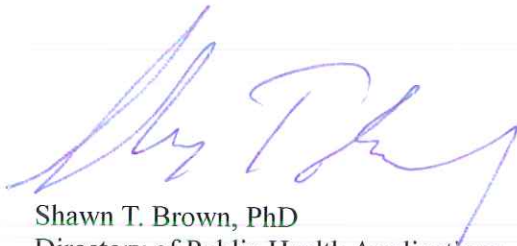
Emily Bancroft
Program Director, Health Systems Group Lead

Bruce Y. Lee, MD MBA
Associate Professor
Director of Operations Research, International Vaccine Access Center
Department of International Health
Johns Hopkins Bloomberg School of Public Health
855 N. Wolfe Street
Baltimore, MD 21205

Dear Dr. Lee,

On behalf of myself and the Pittsburgh Supercomputing Center, I am extremely pleased and excited to continue our longstanding collaboration by embarking on the proposed work “Strategic Immunization Geotemporal Mapping Application (SIGMA)”. The Pittsburgh Supercomputing Center is committed to developing the SIGMA platform for understanding and improving adult immunization logistics. Our center’s nearly 7 year collaboration with Dr. Lee and his team has been very productive, and this is yet another exciting opportunity for us to continue using modeling and technology to strengthen health systems. We look forward to working with your team on this important public health issue and will dedicate our team and resources fully to this project.

Sincerely,



Shawn T. Brown, PhD
Directory of Public Health Applications
Pittsburgh Supercomputing Center
Carnegie Mellon University
stbrown@psc.edu

H. Bibliography

1. Haidari LA, Connor DL, Wateska AR, Brown ST, Mueller LE, Norman BA, Schmitz MM, Paul P, Rajgopal J, Welling JS, Leonard J, Chen SI, **Lee BY**. Augmenting transport versus increasing cold storage to improve vaccine supply chains. *PLoS one* 2013;8:e64303.
2. Everett KH, Potter MA, Wheaton WD, Gleason SM, Brown ST, **Lee BY**. Geospatial analytics to evaluate point-of-dispensing sites for mass immunizations in Allegheny County, Pennsylvania. *Journal of public health management and practice : JPHMP* 2013;19 Suppl 2:S31-6.
3. Norman BA, Nourollahi S, Chen SI, Brown ST, Claypool EG, Connor DL, Schmitz MM, Rajgopal J, Wateska AR, **Lee BY**. A passive cold storage device economic model to evaluate selected immunization location scenarios. *Vaccine* 2013;31:5232-8.
4. Assi TM, Brown ST, Kone S, Norman BA, Djibo A, Connor DL, Wateska AR, Rajgopal J, Slayton RB, **Lee BY**. Removing the regional level from the Niger vaccine supply chain. *Vaccine* 2013;31:2828-34.
5. Smith KJ, Wateska AR, Nowalk MP, Raymund M, **Lee BY**, Zimmerman RK. Modeling of cost effectiveness of pneumococcal conjugate vaccination strategies in U.S. older adults. *American journal of preventive medicine* 2013;44:373-81.
6. **Lee BY**, Bartsch SM, Willig AM. The economic value of a quadrivalent versus trivalent influenza vaccine. *Vaccine* 2012;30:7443-6.
7. Bartsch SM, Lopman BA, Hall AJ, Parashar UD, **Lee BY**. The potential economic value of a human norovirus vaccine for the United States. *Vaccine* 2012;30:7097-104.
8. **Lee BY**, Cakouros BE, Assi TM, Connor DL, Welling J, Kone S, Djibo A, Wateska AR, Pierre L, Brown ST. The impact of making vaccines thermostable in Niger's vaccine supply chain. *Vaccine* 2012;30:5637-43.
9. **Lee BY**, Bacon KM, Wateska AR, Bottazzi ME, Dumonteil E, Hotez PJ. Modeling the economic value of a Chagas' disease therapeutic vaccine. *Human vaccines & immunotherapeutics* 2012;8:1293-301.
10. Assi TM, Rookkapan K, Rajgopal J, Sornsrivichai V, Brown ST, Welling JS, Norman BA, Connor DL, Chen SI, Slayton RB, Laosiritaworn Y, Wateska AR, Wisniewski SR, **Lee BY**. How influenza vaccination policy may affect vaccine logistics. *Vaccine* 2012;30:4517-23.
11. **Lee BY**, Bacon KM, Shah M, Kitchen SB, Connor DL, Slayton RB. The economic value of a visceral leishmaniasis vaccine in Bihar state, India. *The American journal of tropical medicine and hygiene* 2012;86:417-25.
12. **Lee BY**, Assi TM, Rookkapan K, Wateska AR, Rajgopal J, Sornsrivichai V, Chen SI, Brown ST, Welling J, Norman BA, Connor DL, Bailey RR, Jana A, Van Panhuis WG, Burke DS. Maintaining vaccine delivery following the introduction of the rotavirus and pneumococcal vaccines in Thailand. *PLoS one* 2011;6:e24673.
13. **Lee BY**, Tai JH, McGlone SM, Bailey RR, Wateska AR, Zimmer SM, Zimmerman RK, Wagner MM. The potential economic value of a 'universal' (multi-year) influenza vaccine. *Influenza and other respiratory viruses* 2012;6:167-75.
14. Assi TM, Brown ST, Djibo A, Norman BA, Rajgopal J, Welling JS, Chen SI, Bailey RR, Kone S, Kenea H, Connor DL, Wateska AR, Jana A, Wisniewski SR, Van Panhuis WG, Burke DS, **Lee**

- BY.** Impact of changing the measles vaccine vial size on Niger's vaccine supply chain: a computational model. *BMC public health* 2011;11:425.
15. **Lee BY,** Brown ST, Bailey RR, Zimmerman RK, Potter MA, McGlone SM, Cooley PC, Grefenstette JJ, Zimmer SM, Wheaton WD, Quinn SC, Voorhees RE, Burke DS. The benefits to all of ensuring equal and timely access to influenza vaccines in poor communities. *Health affairs (Project Hope)* 2011;30:1141-50.
 16. **Lee BY,** Assi TM, Rookkapan K, Connor DL, Rajgopal J, Sornsrivichai V, Brown ST, Welling JS, Norman BA, Chen SI, Bailey RR, Wiringa AE, Wateska AR, Jana A, Van Panhuis WG, Burke DS. Replacing the measles ten-dose vaccine presentation with the single-dose presentation in Thailand. *Vaccine* 2011;29:3811-7.
 17. **Lee BY,** Assi TM, Rajgopal J, Norman BA, Chen SI, Brown ST, Slayton RB, Kone S, Kenea H, Welling JS, Connor DL, Wateska AR, Jana A, Wiringa AE, Van Panhuis WG, Burke DS. Impact of introducing the pneumococcal and rotavirus vaccines into the routine immunization program in Niger. *American journal of public health* 2012;102:269-76.
 18. **Lee BY,** Bacon KM, Bailey R, Wiringa AE, Smith KJ. The potential economic value of a hookworm vaccine. *Vaccine* 2011;29:1201-10.
 19. **Lee BY,** Bacon KM, Connor DL, Willig AM, Bailey RR. The potential economic value of a *Trypanosoma cruzi* (Chagas disease) vaccine in Latin America. *PLoS neglected tropical diseases* 2010;4:e916.
 20. **Lee BY,** Wateska AR, Bailey RR, Tai JH, Bacon KM, Smith KJ. Forecasting the economic value of an Enterovirus 71 (EV71) vaccine. *Vaccine* 2010;28:7731-6.
 21. Smith KJ, **Lee BY,** Nowalk MP, Raymund M, Zimmerman RK. Cost-effectiveness of dual influenza and pneumococcal vaccination in 50-year-olds. *Vaccine* 2010;28:7620-5.
 22. **Lee BY,** Brown ST, Cooley P, Grefenstette JJ, Zimmerman RK, Zimmer SM, Potter MA, Rosenfeld R, Wheaton WD, Wiringa AE, Bacon KM, Burke DS. Vaccination deep into a pandemic wave potential mechanisms for a "third wave" and the impact of vaccination. *American journal of preventive medicine* 2010;39:e21-9.
 23. **Lee BY,** Bailey RR, Wiringa AE, Afriyie A, Wateska AR, Smith KJ, Zimmerman RK. Economics of employer-sponsored workplace vaccination to prevent pandemic and seasonal influenza. *Vaccine* 2010;28:5952-9.
 24. **Lee BY,** Popovich MJ, Tian Y, Bailey RR, Ufberg PJ, Wiringa AE, Muder RR. The potential value of *Clostridium difficile* vaccine: an economic computer simulation model. *Vaccine* 2010;28:5245-53.
 25. **Lee BY,** Brown ST, Korch GW, Cooley PC, Zimmerman RK, Wheaton WD, Zimmer SM, Grefenstette JJ, Bailey RR, Assi TM, Burke DS. A computer simulation of vaccine prioritization, allocation, and rationing during the 2009 H1N1 influenza pandemic. *Vaccine* 2010;28:4875-9.
 26. **Lee BY,** Norman BA, Assi TM, Chen SI, Bailey RR, Rajgopal J, Brown ST, Wiringa AE, Burke DS. Single versus multi-dose vaccine vials: an economic computational model. *Vaccine* 2010;28:5292-300.
 27. **Lee BY,** Ufberg PJ, Bailey RR, Wiringa AE, Smith KJ, Nowalk AJ, Higgins C, Wateska AR, Muder RR. The potential economic value of a *Staphylococcus aureus* vaccine for neonates. *Vaccine* 2010;28:4653-60.
 28. **Lee BY,** McGlone SM. Pricing of new vaccines. *Human vaccines* 2010;6:619-26.

29. **Lee BY**, Wiringa AE, Bailey RR, Lewis GJ, Feura J, Muder RR. Staphylococcus aureus vaccine for orthopedic patients: an economic model and analysis. *Vaccine* 2010;28:2465-71.
30. **Lee BY**, Tai JH, Bailey RR, Smith KJ, Nowalk AJ. Economics of influenza vaccine administration timing for children. *The American journal of managed care* 2010;16:e75-e85.
31. Beigi RH, Wiringa AE, Bailey RR, Assi TM, **Lee BY**. Economic value of seasonal and pandemic influenza vaccination during pregnancy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009;49:1784-92.
32. **Lee BY**, Tai JH, Bailey RR, Smith KJ. The timing of influenza vaccination for older adults (65 years and older). *Vaccine* 2009;27:7110-5.
33. **Lee BY**, Mehrotra A, Burns RM, Harris KM. Alternative vaccination locations: who uses them and can they increase flu vaccination rates? *Vaccine* 2009;27:4252-6.
34. **Lee BY**, Bartsch SM, Wong KF, Yilmaz SL, Avery TR, Singh A, Song Y, Kim DS, Brown ST, Potter MA, Platt R, Huang SS. Simulation shows hospitals that cooperate on infection control obtain better results than hospitals acting alone. *Health Aff (Millwood)* 2012;31:2295-303.
35. **Lee BY**, Ercius AK, Smith KJ. A predictive model of the economic effects of an influenza vaccine adjuvant for the older adult (age 65 and over) population. *Vaccine* 2009;27:2251-7.
36. **Lee BY**, Bacon KM, Donohue JM, Wiringa AE, Bailey RR, Zimmerman RK. From the patient perspective: the economic value of seasonal and H1N1 influenza vaccination. *Vaccine* 2011;29:2149-58.
37. Haidari LA, Connor DL, Wateska AR, Brown ST, Mueller LE, Norman BA, Schmitz MM, Paul P, Rajgopal J, Welling JS, Leonard J, Claypool EG, Weng YT, Chen SI, **Lee BY**. Only adding stationary storage to vaccine supply chains may create and worsen transport bottlenecks. *Journal of public health management and practice : JPHMP* 2013;19 Suppl 2:S65-7.
38. **Lee BY**, Burke DS. Constructing target product profiles (TPPs) to help vaccines overcome post-approval obstacles. *Vaccine* 2010;28:2806-9.
39. Rajgopal J, Connor DL, Assi TM, Norman BA, Chen SI, Bailey RR, Long AR, Wateska AR, Bacon KM, Brown ST, Burke DS, **Lee BY**. The optimal number of routine vaccines to order at health clinics in low or middle income countries. *Vaccine* 2011;29:5512-8.
40. **Lee BY**, Stalter RM, Bacon KM, Tai JH, Bailey RR, Zimmer SM, Wagner MM. Cost-effectiveness of adjuvanted versus nonadjuvanted influenza vaccine in adult hemodialysis patients. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2011;57:724-32.
41. **Lee BY**, Haidari LA, Lee MS. Modelling during an emergency: the 2009 H1N1 influenza pandemic. *Clin Microbiol Infect* 2013.
42. **Lee BY**, Tai JH, McGlone SM, Bailey RR, Wateska AR, Zimmer SM, Zimmerman RK, Wagner MM. The potential economic value of a 'universal' (multi-year) influenza vaccine. *Influenza Other Respi Viruses* 2012;6:167-75.
43. Balk DL, Deichmann U, Yetman G, Pozzi F, Hay SI, Nelson A. Determining Global Population Distribution: Methods, Applications and Data. *Advances in Parasitology* 2006;62:119-56.
44. Center for International Earth Science Information Network - CIESIN - Columbia University, International Food Policy Research Institute - IFPRI, The World Bank, Centro Internacional de Agricultura Tropical - CIAT. Global Rural-Urban Mapping Project, Version 1 (GRUMPv1): Urban Extents Grid. Palisades, NY: NASA Socioeconomic Data and Applications Center (SEDAC); 2011.

45. 2014 World Development Indicators. Washington, DC: The World Bank; 2014.
46. Walker DG, Hutubessy R, Beutels P. WHO Guide for standardisation of economic evaluations of immunization programmes. *Vaccine* 2010;28:2356-9.
47. The Global Burden of Disease 2004 Update. Geneva: World Health Organization; 2004.
48. Murray CJL, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, MA: Harvard University Press.