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Selecting Malaria Interventions: A top-down approach

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Abstract

Malaria continues to be a great burden on both morbidity and mortality as well as economic development across the world. In highly endemic areas, such as Nigeria, malaria can claim hundreds of thousands of lives and millions of dollars yearly. Typically, when selecting intervention strategies to control malaria, research is focused on the cost-effectiveness and general applicability of individual interventions. In separate studies, great care is taken to develop high-fidelity models of malaria’s economic and morbidity/mortality burden. In this paper, we take a top-down approach to selecting malaria intervention strategies. Instead of studying each element of the problem separately, we combine models for intervention cost-effectiveness, disease burden, and intervention delivery to create a single large-scale geographic optimization. We illustrate our top-down approach with a case study of malaria in Nigeria. Our optimization produces detailed geographic intervention plans, identifies key budget values and specifies the locations of the supply distribution centers.

Keywords: malaria intervention, computing disease intervention strategies, integrated disease model, supply center locations

1. Introduction

Selecting malaria intervention strategies is a complex problem, but one that is highly motivated by the disease’s great burden on economic development and human
morbidity and mortality. Most studies take a bottom-up approach in addressing the problem. They concentrate on a single subproblem in great detail, such as modeling the economic burden of malaria, or studying the cost-effectiveness of a single intervention. In this study, we take a top-down approach, by combining the subproblems into a single large-scale geographic optimization for selecting malaria interventions.

At a high level, our optimization takes as input 1) data on available intervention strategies 2) ecological and demographic data and 3) an intervention budget constraint. As output, the optimization delivers the location of the supply distribution centers and a geographic plan of intervention delivery that minimizes the disease’s impact, subject to the budget constraint. The optimization can be used to construct an efficient frontier, depicting the achievable morbidity or mortality at each budget value.

Geographic epidemiological intervention models have been studied in the past. Most of these models consider a small number of intervention strategies (typically less than 5), e.g., contact tracing and quarantine, and then simulate their effect across the entire geographic region [1, 2, 3, 4]. Large-scale intervention optimization, where a combinatorially large set of intervention strategies is considered is an active area of research. Recently, large-scale intervention optimization has addressed the distribution of a limited stockpile of vaccines to halt pandemic influenza [5], however that study is not geographically targeted. Little work exists in the area of geographically targeted, large-scale intervention optimization [6]; despite explicit calls for the computation of geographically targeted malaria interventions [7]. This paper’s main contribution is a novel large-scale, geographically targeted malaria intervention decision support tool, derived using a top-down approach. The output of the optimization model is a fine-grained geographic intervention plan, specifying a set of actions for each geographic sub-region.

While our top-down optimization approach is able to produce detailed geographic intervention plans, it should be regarded simply as a decision support tool. The complexity and main contribution of a top-down approach comes in combining subproblems to produce the final intervention decision. The drawback of a top-down approach is that each subproblem may be considered in less detail than a typical bottom-up study dedicated solely to an individual subproblem. Our optimization attempts to capture as many aspects of the intervention selection problem as is both 1) computationally tractable and 2) reasonably quantifiable. No model or optimization can capture all the salient factors for a problem as complex as malaria, in which even cultural factors may be definitive in determining the effectiveness of an intervention strategy. Expert knowledge is critical to decision-making; the role of decision
support tools is to make the task of decision makers easier by providing quantitative
data on the effects of various strategies.

We structure the rest of the paper as follows. First, in the Materials and Methods
section we outline the structure of our top-down approach. In the Results section,
we cover in detail the execution of the approach for our case study of malaria in
Nigeria. Finally, in the Discussion section, we draw some conclusions.

2. Materials and Methods

In this section we describe our top-down approach in detail. In the first subsection,
we present the stages, i.e., the building blocks of our approach. In the second
subsection, we focus on the mathematical methodology at the core of the optimiza-
tion.

2.1. Stages for a Top-Down Approach

We adopt a top-down approach consisting of five stages, depicted in Figure 1.

1. **First Input Stage.** In this stage, we gather data to populate the model. The
stage consists of three steps:

   (a) The first step is to gather georeferenced ecological and demographic
data. Ecological data may consist of factors such as average, maximum,
and minimum temperatures, precipitation, as well as topological features
like elevation. Demographic data may include population densities, age
structures, and other parameters that influence susceptibility to the dis-
ease. Data on road networks, the location of major airports, and presence
of the disease in the region may also be included.

   (b) The second step is to specify a budget or range of budgets available for
implementing interventions.

   (c) The third step is to specify a set of available intervention actions to be
analyzed.

2. **Second Input Stage.** In the second stage, we gather data on the intervention
actions specified in part (c), first stage. These data include (a) the cost of
each action (b) the effectiveness of the action in reducing disease morbidity
and mortality. Typically, the effect of combined actions is not cumulative, so
when possible, data on the effectiveness of combinations of actions should be
collected. Data collection of this type presents a substantial area of ongoing
and potential research [8].
Figure 1. A top-down approach for geographic disease intervention. The approach consists of five stages. At the first stage, we collect georeferenced ecological and demographic data; a budget limit for intervention (if available); and a set of actions available for intervention. At the second stage, we gather data on the costs and effects of the available actions. The third stage incorporates spatial disease risk, implementation cost, and disease impact models. At the fourth stage, an optimization model selects the best set of intervention actions and the best location for the supply distribution centers. At the fifth stage, we output suggested intervention strategies and the locations of the supply distribution centers.
3. **Modeling.** The models listed below will be used for computing the cost and effectiveness of possible intervention plans. We include the following models: (a) a disease risk model across the geographic region (b) a distribution cost model to capture the costs of implementing intervention actions across the region (c) an impact model of the disease on the economy and morbidity/mortality. Developing such models has attracted substantial research efforts [9, 10, 11, 12]. These models are necessary to identify the objective function of the optimization.

4. **Optimization.** In this stage, we perform the core optimization of the top-down approach. The optimization is concerned with two related issues: making initial design choices on the location of the supply distribution centers and selecting the best intervention strategy across the geographic region. The optimization model is guided by the disease risk model, distribution cost model, and impact model from stage three. On the other hand, intervention actions selected by the optimization could change the output of the models in stage three. We depict this two-way interaction with the double-sided arrow in Figure 1. This stage is the core of the top-down approach and is developed in detail in Section 2.2.

5. **Output.** Finally, in the fifth stage, as output from the optimization, we obtain the locations of the supply distribution centers and a set of intervention strategies across the region. The intervention strategies suggested by the optimization model can be analyzed and combined with local expert knowledge to inform decision makers.

### 2.2. Optimization

In the optimization stage we are concerned with two related issues, identifying geographic intervention plans and specifying the locations of the supply distribution centers, which we address in turn.

#### 2.2.1. Intervention Strategies

The optimization method we use to select intervention actions is a special case of a more general Markov Decision Process (MDP) framework [13, 14]. We focus our description on the special case we use rather than the more general framework because it greatly simplifies the presentation. The interested reader can read more about the MDP framework in Dimitrov and Morton [13].

For the remainder of the paper, we fix a time interval of one year, so that all costs, rewards, and actions are on a per-year basis. We start by introducing some notation.
Let the geographic area of interest be divided into a set of cells, \( S \), with \(|S|\) denoting the number of cells in \( S \). Let each cell have a set of available intervention actions to choose from, \( A_s \). Let \( R(s,a) \), for a cell \( s \in S \) and an action \( a \in A_s \), be the reward for performing action \( a \) in cell \( s \), in terms of decrease morbidity or mortality. Similarly, let \( C(s,a) \) be the cost of performing action \( a \) in cell \( s \). Given an allotted budget \( b \), we can formulate the problem of selecting intervention actions subject to a single budget constraint as follows:

\[
\begin{align*}
\text{max} & \quad \sum_{s \in S} \sum_{a \in A_s} R(s,a) y_{s,a} \\
\text{s.t.} & \quad \sum_{s \in S} \sum_{a \in A_s} C(s,a) y_{s,a} \leq b \\
& \quad \sum_{a \in A_s} y_{s,a} = 1, \quad s \in S \\
& \quad y_{s,a} \geq 0, \quad s \in S, a \in A_s,
\end{align*}
\]

where the decision variables, \( y_{s,a} \), represent the fraction of time action \( a \) is performed in cell \( s \). Allowing fractional choices on the actions ensures that the entire budget can be utilized. For example, if there is one very expensive action with an excellent reward, we may choose to use it only a small fraction of the time so that we remain within the budget. It is possible to have a similar model with multiple budget constraints, which can include particular resources besides dollars. With \( m \) budget constraints, it is guaranteed that at most \( m \) cells will have a fractional allocation \([15, 16]\).

Model (1) is highly advantageous for modeling optimization for geographic disease interventions. First, it allows us to incorporate nonlinear dependence of the rewards and costs on the actions. To illustrate this, suppose that we would like to decide whether to use indoor residual spraying (IRS) or long-lasting insecticide treated bed nets (LLIN) or both \{LLIN, IRS\} in a particular cell \( s \). Further, suppose that we have data from prior studies on the effectiveness of IRS, LLIN, and \{IRS, LLIN\} and the effect of using both actions is not simply the additive benefit of using each individually. For example, we may receive a reward of 3 for using solely IRS, a reward of 4 for using solely LLIN, but a reward of 6 for using both LLIN and IRS. The optimization model can capture this nonlinear dependence by setting the available intervention actions \( A_s \) to \{\{IRS, LLIN, IRS, LLIN\}\}, i.e., \{IRS, LLIN\} is treated as a new action, and its exact rewards and costs can be incorporated into the model. Of course, if many singleton interventions are available and we would like to allow the use of every subset of interventions, the model size is exponential in the number of
singleton interventions. Practically, however, this may not be a limiting constraint. For example, in the case study we present, there are only 8 singleton interventions considered, which match well with the real intervention plans in Nigeria [17].

Even though we put forward a general top-down approach, the exact meaning of model (1) will differ on a case-by-case basis. For example, the objective function of model (1) is linear in the decision variables, $y_{s,a}$. If $y_{s,a}$ denotes the fraction of time that action $a$ is performed in cell $s$, there may be additional nonlinearities in terms of the reward as a function of the time that the action is performed. Such a nonlinearity would not be captured by the model. An alternate meaning of the variables $y_{s,a}$ is the fraction of the population in cell $s$ for which action $a$ is performed. In this case, if the rewards across individuals are not dependent, the rewards overall are linear in $y_{s,a}$.

Model (1) can be solved directly using a generalized linear programming solver, however, such an algorithmic approach does not scale to large geographic regions. The run time of a generalized linear programming solver is $O(n \cdot m^2)$, where $n$ is the number of variables in the model ($|S| \cdot |A_s|$) and $m$ is the number of constraints ($|S|$). For our case-study, with more than 269 thousand cells and 18 available actions in each cell, the theoretical run time would be on the order of $3.5 \cdot 10^{16}$ operations. To scale the optimization to large geographic regions, an alternate algorithmic approach is necessary.

The second advantage of model (1) is that it can be solved using a fast greedy algorithm, allowing the optimization to scale beyond hundreds of thousands of individual geographic cells. To see the efficiency of this algorithm, imagine that the budget constraint in model (1) is not present. Then, the model can be easily solved by selecting the action $a \in A_s$ with the greatest reward, $R(s,a)$, for each cell $s$, and setting $y_{s,a} = 1$ and $y_{s,a'} = 0$ for all other $a' \in A_s$. However, when budget constraints are included, the problem does not separate by cell in this manner. Instead, Lagrangian relaxation of model (1) can be used:

$$\max_y \sum_{s \in S} \sum_{a \in A_s} (R(s,a) - \lambda C(s,a))y_{s,a}$$

s.t. $\sum_{a \in A_s} y_{s,a} = 1, \quad s \in S$

$y_{s,a} \geq 0, \quad s \in S, a \in A_s,$

where $\lambda$ is the Lagrange multiplier for the budget constraint. One can think of $\lambda$ as a penalty incurred for overspending the budget. For more on constrained MDPs, see the discussion in [18], and for more specifics on the use of Lagrangian relaxation
for MDPs with a single budget constraint see [19]. MDPs with multiple budget constraints can be solved using standard linear programming algorithms.

In order to solve model (1) via model (2), we must search for the appropriate value of \( \lambda \). A value of \( \lambda \) that is too small leads to a solution that exceeds the budget, and if \( \lambda \) is too big, then we under-utilize the budget. A simple binary search allows us to find the “right” value of \( \lambda \). The advantage of this approach is that, for any fixed value of \( \lambda \), model (2) separates by cell, i.e., it can be solved by the greedy algorithm that simply selects the best action in each cell. Another option is to solve model (2) for a range of values of \( \lambda \) and keep track of the associated rewards and costs. In this way, we can build an efficient frontier of solutions that trade-off rewards and costs.

The run time of solving model (2) for a fixed value of \( \lambda \) is \( O(|S| \cdot |A_s|) \). For our case-study, this translates to about \( 4.8 \cdot 10^6 \) operations. Even though we have to try a handful of \( \lambda \) values in our binary search, this is significantly smaller than the run time of the general linear programming algorithm.

### 2.2.2. Design Decisions on Supply Distribution Centers

Often, we would like to make some initial design choices that enable our subsequent intervention actions. For example, the choice of “good” locations to place supply distribution centers is of importance, because it may enable or disable some actions in some cells. As a more specific example, in our case study, the cost of an intervention action depends linearly on its distance from the nearest distribution center location. Let \( D = \{d_1, d_2, \ldots, d_k\} \) be the set of all possible locations to place supply distribution centers. Let \( \bar{z} = (z_{d_1}, z_{d_2}, \ldots, z_{d_k}) \) be the design decision, where the binary decision variable \( z_{d_i} \) is set to one if a supply distribution center is placed in location \( d_i \) and set to zero otherwise. We can formulate the problem of selecting an appropriate design decision as follows

\[
\begin{align*}
\max_z & \quad h(\bar{z}) \quad \text{(3a)} \\
\text{s.t.} & \quad \sum_{d \in D} z_d \leq b' \quad \text{(3b)} \\
& \quad z_d \in \{0, 1\}, d \in D, \quad \text{(3c)}
\end{align*}
\]
where

\[
\begin{align*}
    h(z) &= \max_y \sum_{s \in S} \sum_{a \in A_s} R(s, a) y_{s,a} \\
    \text{s.t.} \quad & \sum_{s \in S} \sum_{a \in A_s} C(s, a) y_{s,a} \leq b \\
    & \sum_{a \in A_s} y_{s,a} = 1, \quad s \in S \\
    & y_{s,a} \geq 0, \quad s \in S, a \in A_s \\
    & y_{s,a} \leq z_d, \quad \text{for } (s, a) \text{ enabled by design decision } d.
\end{align*}
\]

(4)

We can interpret this formulation as follows. Constraint (3b) describes which design decision \( z \) we are allowed to take. For example, when placing distribution centers, we may only have the option of selecting \( b' \) centers, leading to a constraint of the form (3b). More complex interplay between the design decisions can be captured with further constraints on the variables \( z \). A given design decision \( z \) is evaluated using the objective function \( h(z) \), which captures the optimal selection of intervention actions given \( z \). In specific, the last constraint of model (4) enforces that the only actions available are those allowed by the selected design decision.

It is also possible to write models (3) and (4) as a single maximization problem over both variables \( z \) and \( y \), by including all the constraints of both models. However, there is a conceptual advantage to split the problem into two parts as presented. As presented, first, the design decisions \( z \) are made, through model (3). Second, based on and constrained by the design decisions, the system is operated, through model (4). Indeed, such a conceptualization allows for a natural algorithmic representation in terms of decomposition algorithms, where a master problem creates a solution \( z \), and a subproblem produces a cut.

For our study of malaria in Nigeria, we consider both issues, selecting intervention actions and identifying the locations of supply distribution centers.

3. Results: A Case Study of Malaria in Nigeria

We illustrate the top-down approach by considering malaria intervention in Nigeria. In each of the following subsections, we describe the stages of the approach as applied to this case study.

3.1. First Input Stage

Ecological and demographic data. We use a 1 arc-minute grid to divide Nigeria into 269,228 cells. For geographic data, we obtained a set of 16 environmental
<table>
<thead>
<tr>
<th>Ecological parameters for case study</th>
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<tbody>
<tr>
<td>Annual Mean Temperature</td>
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<td>Mean Diurnal Temperature Range</td>
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<tr>
<td>Temperature Seasonality</td>
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<tr>
<td>Max Temperature of Warmest Month</td>
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<tr>
<td>Min Temperature of Coldest Month</td>
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<tr>
<td>Temperature Annual Range</td>
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<tr>
<td>Mean Temperature of Warmest Quarter</td>
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<td>Mean Temperature of Coldest Quarter</td>
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<tr>
<td>Annual Precipitation</td>
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<tr>
<td>Precipitation of Wettest Month</td>
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<tr>
<td>Precipitation of Driest Month</td>
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<tr>
<td>Precipitation Seasonality (Coefficient of Variation)</td>
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<tr>
<td>Precipitation of Wettest Quarter</td>
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<tr>
<td>Precipitation of Driest Quarter</td>
</tr>
<tr>
<td>Altitude</td>
</tr>
<tr>
<td>Distance to the Nearest River</td>
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</tbody>
</table>

**Table 1.** This table lists the 16 environmental parameters used in the case study. The data for all parameters, except “Distance to the Nearest River” were gathered from the WorldClim database [20]. The data for “Distance to the Nearest River” was gathered from data of the United States Geological Service [21].
parameters from the WorldClim database [20] and from the United States Geological Service [21], both are publicly accessible as are the remaining sources we cite. Table 1 lists these parameters. These data were available at a resolution of 30 arc-seconds and were resampled at a resolution of 1 arc-minute.

For demographic data, we use human population density data obtained from the Gridded Population of the World Database [22]. These data were available at a resolution of 2.5 arc-minutes and were resampled at a resolution of 1 arc-minute. Multiplying the human population density with the total Nigerian population, we calculate the population of each cell [23]. Malaria mortality is highest among children under the age of five and pregnant women, while infection in other individuals usually results in only limited morbidity due to acquired immunity [24]. Thus, we characterized at-risk groups in the population as children under the age of 5 (17% of the population) and pregnant women (3% of the population) [25]. The economic impact model requires that we know the people in the population that directly contribute to the country’s economy. We defined a “worker” as a person over the age of 14 and computed the fraction of workers in the population (56%) [25]. We assumed that these fractions are constant across the region, to calculate the number of children, pregnant women, and workers in each cell.

**Budget constraints.** No canonical budget estimate was available for potential malaria control in Nigeria. For illustrative purposes, we build an efficiency frontier by analyzing a range of different budgets. The results of such an analysis may help policy makers set budgets from within this range by quantifying the success that can be achieved at each budget level.

**Available actions.** We include 18 actions for disease intervention, including long-lasting insecticide-treated bed nets (LLIN), indoor residual spraying (IRS), intermittent preventative therapy (IPT), artemisinin-based combination therapy (ACT), and rapid diagnostic tests (RDT). Because the effects of actions are not always cumulative, we include some, but not all combinations of actions. Table 2 lists all available actions. We do not include, for example, the combination of LLIN and IRS, since both target the prevention of malaria infection in the home (the pre-bite period). On the other hand, we do include the combination of LLIN and ACT, since the first targets prevention of malaria infection (the pre-bite period), and the second combats the malaria once it is present (the post-bite period). While we also include the combination of IPT and LLIN, assuming cumulative effects, the true effectiveness of this and other combinations of these actions remains to be measured. Also, we split the ACT action into two types: ACT given only to children under 5 (ACT\_under\_5) and ACT given to everyone (ACT\_all). This is in accordance with the identification of children under 5 as an at-risk group.
Table 2. This table lists the 18 available actions in the case study. There are five basic actions: long-lasting insecticide-treated bed nets (LLIN), indoor residual spraying (IRS), intermittent preventative therapy (IPT), artemisinin-based combination therapy (ACT), and rapid diagnostic tests (RDT). Each of these actions targets either the pre-bite period (e.g., stopping the likelihood of a bite), the diagnostic period (e.g., diagnosing malaria over a different disease), or the post-bite period (e.g., lowering the effects of an infection). In addition, each action targets one of three disjoint segments of the population: Children (C), Pregnant Women (W), or the rest of the population (A). In the illustration, due to lack of data on the interactions between actions, we only include combinations of the basic actions that do not affect the same segment of the population in the same period.
3.2. Second Input Stage

**Action cost estimates.** Purchase cost estimates were obtained from the WHO’s Global Malaria Programme [26]. For example, we used their data to specify a purchase cost of 5 USD for LLIN to protect 2 people for 3 years. This gives a purchase cost of 0.83 USD for LLIN per person per year. Similarly, for IRS, we obtained a purchase cost of 6.5 USD for insecticide for a household with 6 people as well as purchase and maintenance costs for spray pumps as detailed in Kiszewsky et al. [26, 27]. This gives a purchase cost of 1.08 USD for IRS per person per year. All other purchase costs were similarly computed.

**Action effect estimates on morbidity/mortality.** First, the consequences of malaria are quantified if no action is taken. In this case study, we model deaths as being restricted to young children (at most 5 years) and pregnant women. The conditional probabilities that infection would result in mortality in children under 5 and pregnant women, 0.035 [28] and 0.030 [29] respectively, were reported in previous studies. In the case study, infections can cause productivity loss for the population at large. We used 4 days of lost productivity and 3 days of half-productivity for an adult’s illness, and one third of those values for a child’s illness [30]. We computed the fraction of infected individuals in each cell as follows.

(a) First we estimated the annual entomological inoculation rate (EIR), which is the number of infective bites per person per year in a given area [31]. Let \( R_i \) represent the EIR of cell \( i \).

(b) Next, the EIR values were used to produce the proportion of infected individuals, say \( I_i \), within each cell using a relationship between these values reported by Beier et al. [32]. The relationship between \( R_i \) and \( I_i \) is then given by

\[
I_i = 24.2 \log R_i + 24.68. \tag{5}
\]

The reported correlation between these two variables was strong, with \( R^2 = 0.712 \) [32].

Next, the effect of each available intervention action was quantified.

- LLINs have been found to reduce the percentage of infected individuals by 63% [33], which agrees with the 50-75% reported by Kiszewski et al. [26, 27].
- IRS has been found to reduce the percentage of infected individuals in a region by 75% [33]. Note that these values are direct reductions in the number of infected individuals, \( I_i \), as opposed to reductions in the EIR.
- ACTs reduce the chance of death for those infected with malaria by 50% [27, 34]. ACTs reduce the morbidity to 3 days, which is a typical dosage period [35]. There are many artemisinin-based cocktails available and there are ongoing studies to
determine the efficacy of each cocktail [35, 36].

- Rapid diagnostic tests (RDTs) allow increased accuracy in rapid diagnosis. They have been found to reduce further medicinal cost by 25% [37].

- Studies indicate that the effects of IPT differ for women during their first or second pregnancy compared to subsequent pregnancies. For women past the second pregnancy, IPT does not seem to have a statistically significant effect on either maternal or fetal death rates [38]. However, for women in their first or second pregnancy, IPT has been found to reduce the rates of severe anaemia in the mother by 65% [38, 39, 40]. IPT also reduces the rate of perinatal death for mothers in their first or second pregnancy. In this case study, we do not model perinatal deaths and, for simplicity, we assume a 65% reduction in the probability of death for a pregnant mother receiving IPT. This assumption is based on the rate of reduction of severe anaemia; the relationship between this reduction and a decrease in mortality remains conjectural [38]. As expected, this assumption has an effect on the suggested intervention strategies.

3.3. Modeling

Disease risk model. Disease risk modeling is a large and active area of research. Several sophisticated approaches to malaria risk modeling exist in the literature [41, 42, 43, 44, 45, 46, 9, 47, 48]. This case study is only intended as an illustration, so we use a simple, plausible model which, however, has not been statistically tested. To estimate the EIR of each cell, we obtain a set of 193 records of EIR values distributed across Africa [44], with each record georeferenced to the nearest arc-minute. The records are then used to create a multivariate linear regression from the demographic and environmental data to EIR values. The resulting regression model was used to estimate the EIR, $R_i$, in each cell in Nigeria (see Figure 2).

The regression shows EIR estimates to be highest in the coastal areas, while low values are observed in the northeast (see Figure 2). This variation appears to result from both the small mean diurnal temperature range in the coastal regions and from the large yearly amount of rainfall in these regions. Malaria vector abundance is greatest in areas that have consistently high temperatures and precipitation. Thus, the EIR values obtained are compatible with what is known about ecological factors that affect malaria transmission.

Implementation model. Accurately modeling implementation costs is recognized as an important area for research [49]. We modeled a linear increase in the implementation cost with the distance of a cell from the closest urban area. The effect of distance on cost were calculated so as to ensure that the average implementation cost of the action equaled that reported in the literature [27]. Urban areas
Figure 2. Multivariate linear regression used to estimate EIR. Figure 2a depicts the variation in EIR ($R_i$) values across Nigeria, as measured in terms of the number of infective bites per person per year. The regression indicated that the EIR values were largely a function of temperature and precipitation. To show this dependence, Figure 2b depicts the mean diurnal temperature range across Nigeria, while Figure 2c depicts the total precipitation of the driest quarter of the year.
Figure 3. Distribution of population in Nigeria. The values indicate the number of individuals that reside within each 1 arc-minute “square” cell. The circles indicate areas designated as urban for the purpose of calculating the implementation costs.

were defined as those with a population of greater than 3 million individuals: Lagos, Kano, and Ibadan. Figure 3 depicts the variation in population density across Nigeria and identifies the areas that were defined as urban for the purposes of calculating implementation costs.

Mortality and economic impact model. As mentioned in the First Input Stage subsection, malaria mortality is highest among children under the age of five and pregnant women. We modeled malaria mortality as being restricted to children in this age group and to pregnant women. We use the following notation:

- \( C_i \) \([P_i]\) is the number of children under the age of five years [pregnant women] in cell \( i \)
- \( M_C \) \([M_P]\) is the probability that an infected child [pregnant woman] will die
- \( D_i \) is the total number of deaths in cell \( i \).

We assumed that infections are uniformly distributed through the demographic layers of the population. With this assumption, the total number of deaths, \( D_i \), in cell \( i \) is given by

\[
D_i = C_i I_i M_C + P_i I_i M_P,
\]  

where \( I_i \) is obtained using model (5).

As opposed to mortality, which is restricted to young children (at most 5 years) and pregnant women, we assumed morbidity affects the entire population. In order to quantify morbidity we use the following economic impact model. We use the following notation:

- \( W_i \) is the number of workers in cell \( i \) who contribute to the national gross do-
mestic product
- $G$ is the average daily economic contribution of an individual worker
- $L_P [L_C]$ is the average number of days lost as a result of adult [child] illness.

Then, the economic cost $E_i$ due to malaria in cell $i$, again under the assumption that infections are uniformly distributed through demographic layers of the population, is estimated as

$$E_i = W_i I_i G L_P + C_i I_i G L_C, \quad (7)$$

where $I_i$ is given in $(5)$.

3.4. Optimization Model

We populate the parameters of the optimization model as follows. An $A_s$ consists of the 18 intervention actions discussed in the First Input Stage subsection. The available actions are the same for all cells $s \in S$. In our study, the objective function is given by

$$\alpha H \sum_i D_i + (1 - \alpha) \sum_i E_i, \quad (8)$$

with $D_i$ and $E_i$ specified in equations (6) and (7). The parameter $\alpha$, $0 \leq \alpha \leq 1$, represents the relative importance assigned to mortality vs. economic impact. The factor $H$ assigns a monetary value on a human life, so that the terms in (8) are measured with the same units. Setting $\alpha = 1$ gives an objective function solely concerned with mortality, while setting $\alpha = 0$ gives an objective function solely concerned with the economic impact of malaria.

The flow of information to parameterize the optimization model is summarized visually in Figure 4. Models (1) and (2) require three data parameters: $R(s,a)$, $C(s,a)$ and the intervention budget $b$. We parametrically range the intervention budget $b$ over many values, leaving only parameters $R(s,a)$, $C(s,a)$ to be specified.

To specify the parameter $R(s,a)$, the reward for performing action $a$ in cell $s$, we use the following procedure. First, we use estimates of the entomological inoculation rate ($R_i$) derived from the disease risk model to estimate the fraction of infected individuals $I_i$ in each cell, using equation (5). Once we have this fraction, we calculate the number of deaths $D_i$, using equation (6), and productivity loss $E_i$, using equation (7), for each cell. This allows us to calculate a penalty value, specified by formula (8). Performing an action in a cell reduces the penalty, by either reducing the number of infected individuals, the number of deaths, or the productivity loss in the cell. The reduction in the penalty, formula (8), when performing action $a$ in cell $s$ defines a value for the reward $R(s,a)$. For example, if 100 individuals per year die without any interventions, and 80 individuals per year die when intervention action $a$ is performed, the reward for performing the action is 20.
Figure 4. Parameterization Summary. Optimization models (1), (2), (3) and (4) require two key parameters: the rewards for performing an action in a cell, $R(s, a)$, and the cost for performing an action in a cell, $C(s, a)$. Figure 4a summarizes the computation of $R(s, a)$ for the case study of interdicting malaria in Nigeria. Similarly, Figure 4b summarizes the computation of $C(s, a)$ for the case study.
We split the parameter $C(s,a)$, the cost of performing action $a$ in cell $s$ into two parts. The first is the procurement cost associated with the action, and the second is the implementation cost associated with the action. Average action purchase costs and implementation costs per person are available as described in Section 3.2. The implementation costs per person increase linearly with the distance from the nearest distribution center as described in Section 3.3. The purchase cost per person remains the same regardless of the distance from the distribution centers. The sum of purchase cost and implementation cost allows us to compute, the parameter $C(s,a)$, the cost of performing action $a$ in cell $s$. In this way, all parameters of optimization models (1), (2), (3) and (4) are specified, and we can compute solutions.

3.5. Outputs

The suggested intervention strategies for three different objective functions are depicted in Figure 5.

1. The map in Figure 5a shows the suggested strategy for limiting malaria mortality at a selected budget. This corresponds to an objective function (8) with $\alpha = 1$. The different colors in the map represent different actions. A color in a particular area represents the performance of the associated action in that area, as part of the overall intervention strategy. Thus, the map indicates that at a budget of $87.64 \cdot 10^6$ USD per year, the suggested intervention strategy involves the distribution of IPT and ACT to pregnant women and to children under the age of five years, across most of the country. In highly populated areas, these actions are supplemented with IRS and LLIN. The graph in Figure 5a depicts the effects on mortality of adopting the suggested intervention strategies associated with a range of budgets. The $x$-axis indicates the budget, in millions of USD per year, while the $y$-axis indicates the number of deaths from malaria, in thousands per year. The red dot indicates the budget and corresponding number of deaths for the map shown in Figure 5a.

In the study, malaria mortality is assumed to be limited to pregnant women and young children. When the budget is increased, the first strategy to be implemented is IPT, followed by the distribution of ACT to children under the age of five. These suggestions, of course, depend on the effects assumed for these strategies (see the Second Input Stage subsection). Specifically, if we change the effects of IPT, we would see different suggested strategies as output. The case study shows that providing both IPT to pregnant women and ACT to children under five years old, in all relevant areas of Nigeria, costs roughly $17 \cdot 10^6$ USD per year and prevents 290 000 deaths per year, at a cost.
Figure 5. Suggested intervention strategies. Figure 5a depicts both the suggested strategy for limiting malaria mortality at a selected budget, and the effect of adopting the suggested strategy for each of a range of budgets. Figure 5b depicts the same information, but for the minimization of economic impact due to malaria. Figure 5c depicts the results when limiting a mixture of malaria mortality and economic impact. With each of the objectives, at small budgets, strategies were initially targeted to areas of high population density. This reflects the high cost effectiveness of implementing strategies in urban areas. An interesting result of the analysis is the kinks visible in the graphs of Figures 5a and 5b. These kinks represent a decrease in the cost effectiveness of the remaining available strategies as the budget is increased, and can thus be used to indicate critical budget funding levels.
of 60 USD per life saved. The abrupt change of slope in the graph in Figure 5a is located at this budget amount. This kink in the graph can be used as an indicator for critical disease intervention funding levels. As the budget is increased beyond $17 \cdot 10^6$ USD per year, more expensive strategies such as LLIN and IRS are suggested. These strategies are first implemented in the major population centers, as can be seen in Figure 5a. This focus on urban areas is due to the underlying implementation cost model, which gives smaller distribution costs, on a per person basis, in highly populated areas.

2. Figure 5b shows the results when the reward function reflects the reduction of the economic impact of malaria. This corresponds to an objective function (8) with $\alpha = 0$. The format of the figure is identical to that of Figure 5a; however, the effects of adopting the different intervention strategies are presented in terms of lost economic productivity, rather than malaria mortality.

In our case study, at small budget amounts, the economic consequences of malaria infection are reduced through the distribution of LLINs to areas of high population density. As the budget is increased, this strategy is supplemented with IRS in these areas. As the budget is further increased, IRS is distributed throughout the majority of the country. Covering the majority of the country with IRS costs approximately $131 \cdot 10^6$ USD per year and prevents $422 \cdot 10^6$ USD in economic costs. The abrupt change in slope in Figure 5b is located at this budget amount. Similar as in the analysis for minimizing mortality, such an abrupt change in slope can be used to indicate critical funding levels for disease intervention. As the budget is further increased, ACT is distributed to all individuals in areas with high population densities, and elsewhere to children under the age of five. The change in slope seen in Figure 5b reflects the lower efficiency of this strategy, as compared to that of distributing LLINs and IRS. These results again depend on the specifics of our model. For example, if the model were to include further losses due to untreated malaria, it is likely that ACT would become a suggested strategy at much lower budgets.

3. Figure 5c depicts a suggested strategy for a selected budget when minimizing both economic costs and mortality. This corresponds to an objective function (8) with $0 < \alpha < 1$. For this optimization, the conversion factor $H$ must also be specified, which will always be controversial. So as not to endorse any particular such value, Figure 5c represents the effects of assigning an arbitrary economic cost to mortality. For this reason, the graph in Figure 5c is presented in terms of a unitless quantity referred to as “Reward”. This graph indicates that as the budget increases, the suggested strategies exhibit
the combined characteristics of the suggested strategies for limiting mortality ($\alpha = 1$) and economic impact ($\alpha = 0$) individually. At low budget levels, the majority of the country is provided with IPT. As the budget increases, ACT is provided to children under the age of five. However, before the entire country is provided with IPT and ACT, LLINs are distributed to the major population centers, with IRS provided to the outlying areas. As the budget is further increased, IRS and ACT are provided across the country. The model is able to produce results for the assignment of any value to the conversion factor $H$.

In general, a solution to model (1) may involve at most one cell with a fractional choice of action, as there is only one budget constraint. A fractional choice of action may be difficult to implement realistically. On the other hand, there always exists a non-fractional solution to model (2) for each value of $\lambda$. The main drawback of using model (2), however, is that its solutions may over-utilize or under-utilize the intervention budget. As the penalty $\lambda$ in model (2) changes, the budget used experiences discrete jumps. As a practical matter, these discrete jumps are quite small. As an example, the graph in Figure 5a was derived from a total of 520 non-fractional solutions, with an average distance of 0.29 million between solutions (on the x-axis). Similar statements hold for the other two graphs in Figure 5. In such situations, it may be more practical to simply use model (2) to compute intervention strategies that are non-fractional and approximately satisfy the budget constraint.

### 3.6. Locating Supply Distribution Centers

Separately from optimizing intervention actions, we run a second optimization in which we allow the optimization model to select three of Nigeria’s five most populated cities as distribution centers. Figure 6 graphically displays the possible distribution center locations – Lagos, Kano, Ibadan, Kaduna, and Port Harcourt. The implementation cost of an intervention action in a cell depends linearly on the distance to the nearest distribution center location.

In general, for different values of the intervention budget, different locations may be selected. However, in the case study, over a wide range of budgets and objective functions, the optimal distribution center locations did not change, and were consistently the three locations in the coastal areas. Figure 6 graphically displays the locations chosen by the optimization – Lagos, Ibadan, and Port Harcourt. Retrospectively, the clustering of distribution centers around the coastal areas is intuitively plausible as those areas have the greatest malaria prevalence, as pictured in Figure 2a.

For our case study, distribution center locations exclusively affect the implementation costs of intervention strategies (see Figure 4). Selecting suboptimal distribution
Figure 6. Results for selecting distribution center locations. Figure 6a displays the locations of Nigeria’s five most populated cities: Lagos, Kano, Ibadan, Kaduna, and Port Harcourt. The color represents the distance, in arc-minutes, from the nearest city. The optimization is allowed to select three of these to be distribution centers. The distribution costs of intervention strategies depend linearly on the distance to the nearest distribution center. Figure 6b displays the locations selected by the optimization. The color represents the distance from the nearest distribution center in arc-minutes. Even though the optimization is run separately for different budgets and objective functions, Lagos, Ibadan, and Port Harcourt are consistently selected as distribution centers. Retrospectively, this selection is intuitive as the distribution centers are targeted towards the coastal areas, where malaria is most prevalent (see Figure 2).
center locations makes some desirable implementation plans too expensive for the available budget. For most intervention actions, average implementation costs are approximately 10% of purchasing costs [27]. We observe approximately 2% change in the objective function value when poor distribution center locations are selected. In other applications, the impact of distribution center locations could be more significant, because it could alter the availability of intervention actions in specific geographic areas.

4. Discussion

We propose a top-down approach for suggesting disease intervention strategies across a given geographic region. A top-down approach combines models for many subproblems into one. In contrast, most studies take a bottom-up approach, where a detailed model for a single subproblem is developed. The benefit of a top-down approach is that it results in a decision support tool. The drawback of a top-down approach is that to maintain tractability, often, the models for each of the individual subproblems are necessarily simpler than in a bottom-up study.

Our top-down approach, as presented in Figure 1, consists of sequential stages, and each stage consists of several steps that are largely independent of each other. In addition, we describe an optimization approach, model (2), that is efficient and scales to large geographic regions. In contrast, naive approaches to solving the optimization would be computationally unable to suggest fine-grained intervention plans for large regions.

We provide an explicit example of the top-down approach with a case study of intervention against malaria in Nigeria. The data manipulation, modeling, and visualization of results using geographic information systems are all carried out using Python and its related open source libraries [50, 51, 52]. Our analysis reveals some interesting aspects of the problem.

1. Figure 5 shows that there are particular budget values at which the marginal effect of increasing the budget drastically changes. Such “critical” values may be used to choose appropriate budget allocations for intervention, given limited budgets and multiple demands to control other diseases.

2. The case study also shows that, at certain budget levels, a good strategy is to use a single intervention method (IRS, for example) for the entire geographic region. While this is somewhat unexpected, since strategies involving multiple intervention techniques are widely thought to be optimal [53], it can be explained by the budget constraint in the optimization. At times, the budget simply allows only for a certain cheap action to be selected, and it is better to
cover the entire region with that single action than to leave some areas without intervention and cover others with multiple interventions.

3. The case study suggests that covering the region uniformly with distribution centers may not be the best strategy. Instead, it is better to place distribution centers in locations where the disease is most prevalent. This result is likely to be robust in the sense that more, or better-quality, data are not likely to affect the conclusion. The result is also intuitively plausible, since distribution centers should track disease risk and human population density, neither of which is uniformly spatially distributed.

In Table 3, we point out refinements that would increase the fidelity of our analysis. Some of these refinements can be easily incorporated, while others would take considerably more effort. For example, using more sophisticated spatial models of malaria risk across Nigeria based on region-specific disease incidence data or vector distributions, could be easily incorporated. On the other hand, incorporating the effects of seasonality, environmental control actions, or the inclusion of movement of both insect vectors [54] and human hosts [55, 56] would require the formulation of a full-fledged MDP model or an alternate optimization model. This would likely require significantly more input data and computation time.

It is administratively infeasible to implement 200,000 separate actions, one in each cell. There are two ways to address this practical concern. First, the optimization may be performed with a geographic partition based on sensible local administrative and geographic boundaries instead of gridded geographic areas. Second, allowing the decision support tool to optimize over a fine geographic partition can provide decision makers with valuable insight on the naturally occurring high-level structure of the resulting solutions. For example, because of the homogeneity in the underlying factors for adjacent cells, the maps in Figure 5 suggest that solution structure can be roughly split based on three geographic areas: high population density close to a distribution center, medium to high population density at a medium distance from a distribution center, and low population density at significant distance from a distribution center. The optimization results provide insights on the dominant strategies in these areas. Another example of a high-level, post-facto intuitive solution structure is item 3 above, on good distribution center locations. Such insights can help decision makers design good, implementable intervention plans.

The practical implementation of any intervention strategy would have both agreements and disagreements with an optimized model such as the one presented here. For example, the Nigerian Federal Ministry of Health’s National Malaria Control Programme [57, 17] focuses on the same sets of actions identified in this study: LLIN, IRS, ACT (often split to children under 5 and older groups), IPT to pregnant women,
<table>
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<th>Section</th>
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<tr>
<td>Demographic data</td>
<td>Including more detailed demographic breakdown for each cell, as opposed to assuming uniform frequencies for children, pregnant women, and workers, would help target interventions.</td>
</tr>
<tr>
<td>Available actions</td>
<td>Including a stronger feedback mechanism between the optimization model and the disease risk model would allow for the inclusion environmental control actions such as spraying large areas with insecticide, drainage, vegetation clearance, and larviciding.</td>
</tr>
<tr>
<td>Effect estimates</td>
<td>Incorporating results of direct studies on the effect of combinations of interventions, as opposed to assuming additive effects for some combinations and omitting others, would significantly improve the fidelity of the model.</td>
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<td>Disease risk model</td>
<td>Using more sophisticated techniques from the malaria risk modeling literature [41, 42, 43, 44, 60, 45, 9, 47, 48], along with EIR data specific to Nigeria would increase the fidelity of the disease risk model [61].</td>
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<tr>
<td>Implementation cost model</td>
<td>Including data on Nigeria’s road network, airport locations, and considering specific storage facilities and supply levels would improve the implementation cost model [49, 62].</td>
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<tr>
<td>Economic impact model</td>
<td>Removing 100,000 workers from the economy, in reality, is not just 100,000 times as bad as removing a single individual. Incorporating nonlinear economic impact models, would be a significant improvement [63, 64]. A further improvement would be to model acquired immunity to malaria [61, p. 263]. Finally, economic impact estimate we use almost certainly underestimates the actual cost of malaria infection [65]; a more detailed cost-of-illness analysis would be an improvement [66].</td>
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**Table 3.** This table lists future refinements to the malaria intervention model. The left-hand-side column lists sections of the approach described in Figure 1, while the right-hand-side lists areas of future refinements.
and RDT. The logistical distribution of interventions such as LLIN plays a big role in the real world implementation. Additional knowledge of the real-world situation would help produce better results. For example, building institutional capacity to carry out IRS is part of Nigeria’s National Malaria Control Programme [17]. Knowing where there is capacity of IRS, and where there is not could inform the model by altering the actions available in those geographic regions. In addition, the decision of where to install capacity for implementing IRS could be implemented in a similar way as distribution centers are located in this study. Finally, any real-world implementation of an intervention strategy would include continued monitoring of the intervention effectiveness. Continued monitoring of intervention actions is a part of Nigeria’s national malaria intervention plan [17] and is an active area of research due to the malaria parasite’s and mosquito vector’s continuous evolution [58, 59].

Our contribution fits into a broader context of computation of disease intervention strategies. The majority of studies on computing disease interventions evaluate a handful of strategies using a simulator. For example, amongst several studies taking a similar approach [1, 3, 4], Ferguson et al. consider 4 different prophylaxis strategies for containing an emerging influenza pandemic [2]. Recently, there have been studies that increase the realism of the optimization by selecting intervention strategies from a combinatorially large set of possibilities. For example, Medlock and Galvani optimize the distribution of a limited stockpile of vaccines to halt pandemic influenza [5]. However, the study of Medlock and Galvani does not consider geographically targeted interventions. Carter et al. explicitly call for the computation of geographically targeted malaria interventions [7]. Our study builds on a nascent area of intervention optimization that considers computing geographically targeted disease intervention strategies from a combinatorially large set of possibilities [6].

The suggested refinements for the case study highlight a limitation of the top-down approach. As we increase the method’s accuracy in capturing contingent details about a disease in a particular geographic region, we also increase the data requirements for parameterization and we may exponentially increase the time required to compute intervention strategies.

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