Bilevel Optimization Model for the Development of Real-Time Strategies to Minimize Epidemic Spreading Risk in Air Traffic Networks

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An understanding is needed of how epidemics spread to new regions via the global air traffic network so that effective strategies for outbreak control can be developed. Various studies have focused on predicting epidemic spread via the complex air traffic network. However, there is a gap in the literature demanding real-time predictive models that exploit the heterogeneous nature of the air travel pattern to optimize decision making among a set of potential control strategies. A bilevel optimization model is proposed to solve the resource allocation problem for an ongoing epidemic spreading via the air traffic network. The upper-level objective is to optimize the distribution of limited resources for epidemic control, and the lower-level simulation model computes the risk posed to the network under possible scenarios. Results from a demonstration network highlight the advantages of this model. A case study evaluates the risk posed by Ebola to the United States through the domestic air traffic network. The results demonstrate the ability of the model to develop real-time strategies that account for the heterogeneous nature of the air traffic network and the complex dynamics of epidemic spread.

The global air travel system provides a means for pathogens to move around the globe faster and farther than ever before. Additionally, a rise in the volume of international air travel has increased the likelihood that travelers will import infections into new regions. Understanding how infectious diseases spread to new regions via the global air traffic network is essential for designing control measures that can mitigate an outbreak.

Previous studies highlighted the importance of the role that air transportation plays in the global spread of epidemics (*1, 2*). In particular, if high-risk locations or flight routes can be identified given the current status of an outbreak, the allocation of intervention and control resources can be optimized to target these locations. However, two elements are essential: (*a*) a model that can quantify the risk levels of various components in the transport system and (*b*) an optimization model for making decisions about the allocation of resources to achieve a specific objective. Furthermore, given the potential scale of infectious disease outbreaks, the range of outbreak control measures available, imposed budgetary constraints that limit the availability of control resources, and the complexity involved in making real-time decisions, optimization techniques are an invaluable tool. However, optimization methods are not currently relied on for designing control strategies in real-time during an epidemic outbreak. This paper addresses this major gap in both the literature and public health policy with the development of a novel optimization-based modeling framework that provides decision support for outbreak control.

The air travel network evaluated in this study is defined by nodes representing regions (e.g., a city) where there are airports and links representing air travel routes between regions. Travel data consisting of routes and volumes are used to define the network structure and the strength of connections between nodes. Because the model is intended for use in real time, regional infection reports are used to define the current state of the outbreak and to compute the future risk posed to each region in the network. Additionally, the resources required for disease intervention and control are assumed to be limited. The objective of the problem is therefore to allocate the affordable resources (which are subject to budget constraints) such that the future risk posed by the outbreak is minimized across the network.

BACKGROUND

Early attempts at using mathematical models to investigate the spread of disease used homogeneous compartment models and assumed a homogeneous population mix. A well-known example is the susceptible–infected–removed epidemic model developed by Kermack and McKendrick (*3*). Models developed later addressed the heterogeneous nature of the infection process by using network representations. In the context of an air transport network, the structure of the network is particularly significant, as some nodes could be more important than others. Guimerà et al. found that the worldwide airline network is a scale-free small-world network, where some hub airports with many connections can have significant effects on epidemic spread (*4*). The small-world structure also means that a route between any two airports requires few transfers.

Development of both simulation-based and analytical epidemic models has been based on travel volume data of the air traffic network. Agent-based simulation models were used to study the spread of severe acute respiratory syndrome (SARS) and influenza in the global air traffic network (*5, 6*). A publicly available agent-based modeling tool was developed by Broeck et al. (*7*), and its performance was assessed by Ajelli et al. (*8*). An analytical model that made use of air travel data was used by Tizzoni et al. to study the H1N1 influenza

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virus (*9*). This was based on the spatial model by Balcan et al. (*10*) and could consider both long-range air travel and local scale travel by other modes (*11*). These models are valuable for modeling and predicting epidemic spread with available air traffic data, although the structure of the air transport network often was not explicitly explored.

The properties of the air traffic network structure were studied more extensively with concepts from the complex network theory field (*12*). These include measures such as node degree (number of links connected to a node), node betweenness (number of shortest paths through a node), and node clustering coefficient (a node's fraction of pairs of neighbors that are directly connected), which are concepts frequently used in the study of social contact network. The work by Barrat et al. (*13*), Guimerà et al. (*4*), and Wu et al. (*14*) analyzed the structure of air traffic networks, but these were not directly tied to modeling and control of epidemic spread.

The work by Gardner et al. (*15*) and Brockmann and Helbing (*16*) explored how the structure of the air traffic network would govern the epidemic spreading process. Gardner et al. used the current epidemic reports and the air traffic network structure to infer the most likely path that an epidemic has taken. Brockmann and Helbing used the air traffic network flow data to explore paths in the network to infer the likelihood that nodes in the network would be infected, given a particular source node. This information was then used to reconstruct the most likely origin of the infection given the current situation. Research was also done into the use of the properties of the air traffic network and outbreak data to predict dengue importation risk of airports (*17, 18*). The approaches used by these models are significant because they combine analysis of the air traffic network with outbreak data.

However, there is a gap in the literature about real-time predictive models and the optimization of control strategies. Some real-time scenario-based models have been developed that use data to infer outbreak patterns in social contact networks (*19–21*), but not in air traffic networks. This paper addresses this gap and proposes a model for real-time risk prediction and constrained resource optimization to aid decision making. An example network is presented to emphasize the limitations of simply targeting nodes with many connections, as well as the potential impact of short-term decision making, that is, optimizing for the immediate future rather than using a strategic approach with the objective of minimizing the system-level risk in the future. A presented case study uses U.S. air traffic network data and 2014 Ebola outbreak data. The case study considers a scenario in which a case of Ebola enters the United States through international travelers and then spreads locally through domestic air travel; the proposed model is applied and evaluated.

In the following sections, the model is defined and its representation explained. The mathematical formulation of the model is then introduced. The model is applied to a demonstration network and in a real network case study. The conclusions from the results and the limitations of the model are then discussed, motivating future extensions.

MODEL DEFINITION

A bilevel network optimization model is proposed to solve the constrained resource allocation problem for an ongoing outbreak with an iterative approach. In the lower-level model, the risk posed to each individual location (e.g., airport, city, and state) within the air transportation network is quantified according to the current state of the outbreak. The upper-level model uses this information to optimize resource allocation to minimize the risk of infection spread for the network at some specified future time.

The objective of the proposed bilevel model is twofold; first, to quantify the risk posed to each node at all future time steps, and second, to use this information to inform epidemic control decisions. Given the current set of infected regions, this model can be used to answer questions such as, what is the risk posed to region X tomorrow, in a week, in a month? Additionally, the proposed model can be used to evaluate how these risk estimates change depending on the control strategies being implemented. Planners must be able to answer such questions to determine optimal allocation of control resources in a given time frame to minimize the harm caused by an outbreak. Specifically, this model can be used to determine reactive control strategies in real time for emerging infectious diseases.

The network modeled is defined by the air traffic system. It is represented as a directed graph $G = (N, E)$, where N is the set of nodes in the network and E is the set of links. Each node i in the network represents a region (e.g., a city) where there is an airport (or airports) and that has population size h_i. A link (i, j) represents a direct air travel route from node i to node j. A weight on each link β_{ij} represents the strength of the travel route connection and is used to define the transmission rate of infection spread between node i and node j. The transmission rate is a function of the passenger travel volume, f_{ij}, the outbreak size at the origin, k_i, and the origin population, h_i. This rate represents the likelihood of at least one infected passenger traveling from origin i to destination j. β_{ij} is not necessarily equal to β_{ji}.

The lower-level problem is used to model the spread of infection through the network, which is a stochastic process. The process is modeled with a discrete-time compartmental simulation model, which defines the state of every node at every time step, $t = 0, 1, 2, 3$. At each time step, every infectious node attempts to infect its susceptible neighbors in the network, referred to here as a trial. A trial is successful between an infection node i and susceptible node j if the infection is spread to the susceptible node, which occurs with a probability β_{ij}. For each future time step, the probability that a given node will become infected is sought. Therefore the infection risk of a node i is defined as $p_{i,t}$, the probability of node i being infected at any point before or at time step t. The infection risk of a node is determined by the set of infected neighbors with links connected to it. For example, if node j is infected at time step $t = 0$, and the transmission rate from node j to node i is $\beta_{ji} = 0.2$, then at time step $t = 1$, node i has a 20% chance of being infected, or $p_{i,1} = 0.2$, if no other infected nodes are connected to node i.

Compartmental models in the set of states considered are susceptible–exposed–infected–removed, susceptible–infected–removed, susceptible–infected–susceptible, and susceptible–infected. These models are traditionally used to model infection spread within a population. In the presented model, the nodes represent regions rather than a single individual, and only susceptible and infected states are considered. An infected node state is representative of the case in which at least one infected individual exists in the region. All noninfected nodes are assumed to be in a susceptible state (i.e., not yet infected). The recovery state is not considered in this model. Therefore, once a node is infected it will stay infected for the rest of the period modeled and will continue to be able to spread infection to its neighbors. This is a simplified epidemic spreading process, but it is valid for a short time frame (i.e., less than the time for an outbreak to be eradicated). This assumption holds true especially in the case of an emerging infectious disease outbreak where no effective vaccine or treatment is available.

The upper-level model selects the optimal control strategy such that the networkwide risk is minimized, where the total risk is defined as the likelihood of infection occurring to each node by a given time, T, summed over all nodes in the network. The control methods considered in this study are assumed to be implemented at the node level, which in turn translates to reducing the transmission rate on all links emanating from the targeted node. This is representative of an airport implementing surveillance and security measures for all passengers. The effect of control is assumed to apply instantaneously at time step $t = 0$ if a node is selected. Allocating resources to any node i will incur a cost associated with the extent of the control. The total amount of available control resources is assumed to be limited and subject to a budget of B. The impact of each control decision is evaluated with the lower-level simulation model. A set of initially infected source nodes A will be specified at time step $t = 0$ (representing a given situation of the outbreak). The infection is then propagated through the network according to the susceptible–infected simulation model, described above, and the selected control strategy. For a single simulation, at each time step the state of each node (infected or susceptible) is known. The simulation is repeated several times, and the expected probability of each node becoming infected at any given time step can be computed.

The contribution of this work is the novel mathematical problem definition and proposed modeling framework. In this study, exhaustive search is used to solve the upper-level problem, that is, to determine the optimal set of nodes for resource allocation, and to motivate the research. Future work will develop more efficient algorithms to solve the upper-level problem.

MATHEMATICAL FORMULATION

The upper-level formulation is as follows:

$$\min \sum_{i \in N} p_{i,T} \tag{1}$$

subject to

$$\sum_{i \in M} g_i(\delta_i) \leq B \tag{2}$$

$$\delta_i \in [0, 1] \qquad \forall i \in M \tag{3}$$

The lower-level formulation is as follows:

$$p_{i,t} = E[X_{i,t}] \qquad \forall i \in N; \forall t \in \{0, \dots, T\} \tag{4}$$

$$\Pr(X_{i,t} = 1) = 1 - (1 - X_{i,t-1}) \prod_{j \in \gamma(i)} (1 - \delta_j \beta_{ji} X_{j,t-1}) \qquad \forall i \in N; \forall t \in \{1, \dots, T\} \tag{5}$$

$$X_{i,0} = 1 \qquad \forall i \in A \tag{6}$$

$$X_{i,0} = 0 \qquad \forall i \in N \setminus A \tag{7}$$

$$X_{i,t} \in \{0, 1\} \qquad \forall i \in N; \forall t \in \{0, \dots, T\} \tag{8}$$

Equations 1 to 3 define the upper-level model. Constraint 3 specifies the domain for the transmission reduction factor δ_i, which represents whether epidemic control is placed on a node $i \in M$, and the extent of the control. The set $M \subseteq N$ represents the set of nodes at which the controls can be placed. When $\delta_i = 1$, no control is placed on node i and the infection transmission rates from i are not changed. However, $0 \leq \delta_i < 1$ represents that control resources are allocated to node i, causing the transmission rate from i to be reduced to its original value multiplied by δ_i. For the upper-level model, δ_i is the independent variable that will be determined by the optimization process. For each decision $\boldsymbol{\delta} = [\delta_i]_{i \in M}$, the reduction will apply to the lower level, which translates to altering the transmission rate for the set of nodes selected from time step $t = 0$. Constraint 2 is the budget constraint and imposes that the total control strategy cost does not exceed the budget, B. This is the main constraint of the model. Without resource constraints, the best strategy would be to implement control measures at all potentially infected locations. However, realistically this is not an affordable decision. Therefore the best locations must be selected for implementing control within a limited budget, which will reduce the overall risk posed to the network over time. The resource cost incurred when placing controls at a node i is a function of the transmission rate reduction factor, δ_i. The function $g_i(\delta_i)$ should reflect that the larger the amount of reduction, the higher the per-unit cost of control resource for a node. For example, $\delta_i = 0$ represents that transmission rate from node i is reduced to zero, which could happen if an airport is shut down, preventing travel activities from this location. This event would be costly, and the cost function $g_i(\delta_i)$ would limit the possibility of this type of strategy. Objective Function 1 minimizes the total infection risk to the network. The infection risk of a node is defined as the probability that this node is infected by time step T, where T represents the time period at which the control strategy will be assessed.

Constraints 4 through 8 define the lower-level simulation model. Constraint 8 indicates the domain of the binary random variable $X_{i,t}$, which represents the state of node i at time t, and is equal to 1 if node i is in the infected state and 0 otherwise. Constraints 7 and 6 give the initial conditions of the system, that is, the state of all nodes in the network at time $t = 0$. The set $A \subseteq N$ is the set of infection source nodes. Constraint 5 gives the probability that the random variable $X_{i,t}$ is equal to 1. This recursive constraint defines how the simulation progresses from one time step to the next. This probability links the decisions at the upper level with the lower-level problem by altering the transmission rate from certain nodes by using the control decision $\boldsymbol{\delta}$, which in turn affects the spreading behavior of the infection in the simulation. Constraint 4 states that the infection risk of node i at any time t is equal to the expected value, $p_{i,t}$, of the random variable $X_{i,t}$.

The probability a node i is infected at time t is 1 if node i is already in the infected state at the previous time step, and the formulation enforces this because in this case $X_{i,t-1} = 1$ and thus $(1 - X_{i,t-1}) = 0$. However, if node i is still susceptible in the previous time step, the probability that it will be infected at t is related to the infection rate of all its infected neighbors since in this case $(1 - X_{i,t-1}) = 1$. The set $\gamma(i)$ is the set of neighboring nodes connected to node i. A neighbor j will not infect node i if it is not infected at the previous time step because $\delta_j \beta_{ji} X_{j,t-1} = 0$, where β_{ji} is the uncontrolled transmission rate from j to i. An infected neighbor will have probability $\delta_j \beta_{ji} X_{j,t-1}$ of infecting node i. Considering all neighbors simultaneously will yield $1 - \prod_{j \in \gamma(i)} (1 - \delta_j \beta_{ji} X_{j,t-1})$ probability of node i being infected.

The choice of functional form of the transmission rate β_{ij} should be based on the length of the time step and the desired input to be considered in each specific implementation of the model. For the case study in this paper, the outbreak size at the origin, k_i, the origin population, h_i, and the passenger flow, f_{ij}, are considered in β_{ij}. These three parameters are given as constants from data input for each node, and $\beta_{ij} = 1 - [1 - (k_i/h_i)]^{f_{ij}}$. It calculates the probability that at least one infected passenger travels from node i to node j at each time step. This is only one possible form of the function, and other forms could be used depending on the actual modeling requirement.

The main contribution of this work is the proposed problem description and mathematical formulation for making real-time outbreak control policy decisions. The lower-level problem requires capturing the true dynamics of population movements over time, which is inherently complex, and certain simplifying assumptions are made, as follows:

1. A node is considered to be infected if any number of individuals in the local populations is infected.
2. For an infected node the outbreak size is defined to be a constant, k_i. This assumption does not capture the dynamic nature of a local outbreak and will be relaxed in future work.
3. In deriving the transmission rate β_{ij} for each link, $\beta_{ij} = 1 - [1 - (k_i/h_i)]^{f_{ij}}$, the probability of an infected and a noninfected person traveling is assumed to be equal. This assumption may be realistic for a disease by which a person is infected but not yet showing symptoms. However, once symptoms persist, an infected person may be less likely to travel. This behavior will be accounted for in future work.

DEMONSTRATION NETWORK

A 10-node network is used to demonstrate the potential benefits of the model. The test network with respective link transmission rates is shown in Figure 1. Further information about the links and transmission rates in this network are provided in Table 1. In this example, the following assumptions hold:

1. The transmission reduction factor is $\delta_i \in \{0.5, 1\}$ for all nodes $i \in M = N$.
2. The cost of control resource is $g_i(\delta_i) = 2(1 - \delta_i)$ for all nodes $i \in M = N$.
3. The budget of control resources is $B = 2$.
4. The infection source node is always node 1.
5. For each node pair i and j there exists a link (i, j) and a link (j, i). All link transmission rates β_{ij} have been defined as a priori, and $\beta_{ij} = \beta_{ji}$.
6. The time step at which the control strategy is assessed is $T = 5$.

Only one link is drawn for every node pair i and j in Figure 1, although there are two links between them in opposite directions with the same transmission rate. Therefore, in this graph every node has the same out-degree (number of outgoing links) as in-degree (number of incoming links).

Assumption 1 forces the transmission reduction factor to take only a value of 0.5 or 1 to simplify the optimization process. That is, once a node is chosen for control, enough resources must be committed to reduce its link transmission rates by 0.5. Combined with

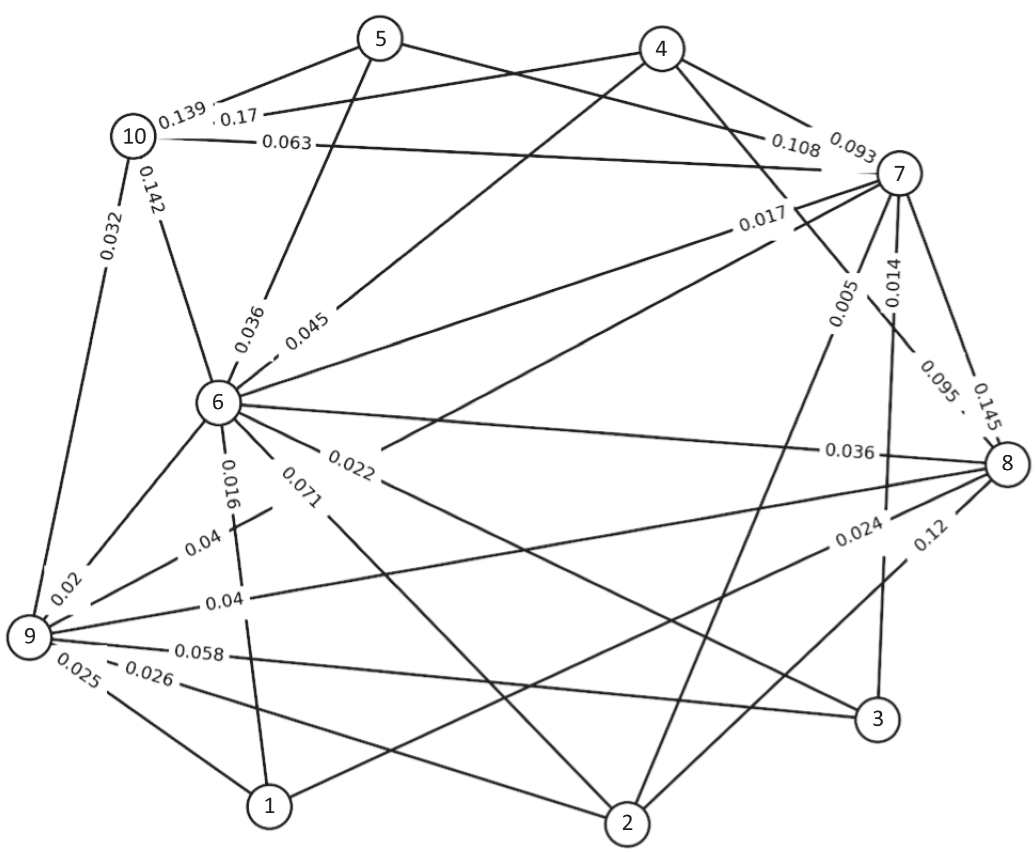

FIGURE 1 Demonstration network with transmission rates.

TABLE 1 Demonstration Network Link Information

Start Node	End Node	Transmission Rate	Start Node	End Node	Transmission Rate
1	6	0.016	7	2	0.005
1	8	0.024	7	3	0.014
1	9	0.025	7	4	0.093
2	6	0.071	7	5	0.108
2	7	0.005	7	6	0.017
2	8	0.120	7	8	0.145
2	9	0.026	7	9	0.040
3	6	0.022	7	10	0.063
3	7	0.014	8	1	0.024
3	9	0.058	8	2	0.120
4	6	0.045	8	4	0.095
4	7	0.093	8	6	0.036
4	8	0.095	8	7	0.145
4	10	0.170	8	9	0.040
5	6	0.036	9	1	0.025
5	7	0.108	9	2	0.026
5	10	0.139	9	3	0.058
6	1	0.016	9	6	0.020
6	2	0.071	9	7	0.040
6	3	0.022	9	8	0.040
6	4	0.045	9	10	0.032
6	5	0.036	10	4	0.170
6	7	0.017	10	5	0.139
6	8	0.036	10	6	0.142
6	9	0.020	10	7	0.063
6	10	0.142	10	9	0.032

Assumption 2, this limitation means that implementing control at any node will always cost one unit of budget. Assumption 3 limits the budget to two units. These three assumptions reduce the upper level of the problem to choosing the set of two nodes that minimize the total risk at the assessment time step in the network. (In this reduced problem, solutions that exhausted the budget always performed better than those that did not.) Assumptions 4, 5, and 6 do not change the complexity of the problem.

In this demonstration, an exhaustive search was used to find the optimal solution for the upper-level model, that is, the strategy that resulted in the lowest systemwide risk. Implementing controls on all possible sets of two-node combination were explored, and the performance of each strategy (i.e., two-node combination) was assessed by running the lower-level simulation 100,000 times. The performance measure used here is $\sum_{i \in N} p_{i,5}$, as defined in the objective function (the likelihood of infection occurring to each node by a given time, summed over all nodes in the network). This number of repetitions provided stable results, that is, the standard deviation of $p_{i,5}$ was smaller than 0.001 for each node, while ensuring the computational burden was not too heavy. Results from the model are shown in Table 2 and are presented in the order of decreasing performance. The Strategy column indicates the set of two nodes chosen, and the networkwide risk of the strategy is presented in the third column. The fourth column contains the difference in risk between the current strategy and the optimal strategy, expressed as a percentage of the optimal strategy risk. Only the strategies including Node 1 are provided because the strategies without Node 1 performed strictly worse. This is an intuitive outcome because reducing the transmission rate at the source is expected to have the most significant effect on the epidemic spread.

TABLE 2 Networkwide Risk for Strategies That Include Node 1

Rank	Strategy (Set of Two Nodes)	Networkwide Risk of Strategy	Percentage Increase in Networkwide Risk (compared with optimal strategy risk)
1	{1, 8}	1.257	0
2	{1, 9}	1.266	0.7
3	{1, 6}	1.267	0.8
4	{1, 10}	1.277	1.6
5	{1, 4}	1.280	1.8
6	{1, 5}	1.281	1.9
7	{1, 2}	1.282	2
8	{1, 7}	1.284	2.2
9	{1, 3}	1.289	2.5

The results show that Nodes 1 and 8 are the optimal nodes to select for control to minimize the total risk at Time Step 5. In this example, Node 6 has a higher degree (in-degree equals out-degree) than Node 8 and is connected to all other nodes in the network. However, implementing control on Node 6 instead of Node 8 resulted in a higher risk posed to the entire network. The results, therefore, demonstrate that simply targeting the nodes with the highest number of connections may not always be an optimal strategy. This is likely an outcome of the transmission rates on the links. The links connected to Node 8 have a high transmission rate. Thus, the outcome highlights the importance of accurately quantifying the link transmission risk, which is a dynamic function of the outbreak evolution within a region, and travel patterns entering and leaving a region. Accurately defining this function will be further explored in future research.

In addition to the expected risk posed to each node, the standard errors of the total risk levels were computed. This was done to ensure that the difference between the rankings of strategies is correct (the difference in computed risk between a {1, 8} set and a {1, 6} set is sufficiently accurate), not a function of stochastic error. To compute the error for each strategy, the total risk level is calculated 100 times (which means $100 \times 100{,}000$ runs of the lower-level simulation). The standard error is 0.002 for set {1, 8} and 0.003 for set {1, 6}. The mean risk levels derived from these 100 runs are 1.256 for set {1, 8} and 1.266 for {1, 6}, which are consistent with the optimization results.

The results of the demonstration show that this model can aid in real-time outbreak control decision making when the availability of control resources is limited and locations for control implementation must be selected from a large set of candidates. In the model, risk is defined at a system level; results indicate that unintuitive strategies may be more effective over time and that these strategies might not be identified without a modeling framework such as that proposed. For example, to optimize for the immediate future, one may instinctively prioritize regions that are directly connected to the source, which would be equivalent to implementing control at Node 9 in this demonstration. However, implementing control at Node 8 is shown to further reduce the risk posed to the network in the long run, although the transmission rate from the source to Node 9 is higher. This outcome reflects that Node 8 has more potential to spread the epidemic if it gets infected. Additionally, the value gained from implementing control at a node is not always directly proportional to the risk of that node being infected in a no-control scenario. For example, the risk of Node 10 being infected is ranked seventh of 10 when no control is placed. However, strategy {1, 10} is ranked fourth of nine according to the optimization model. (Node 1 has no effect on this comparison because control on source affects all nodes to the same extent.)

Finally, because of the system-level approach of this model, multiple possible infection paths are considered, which is significant because of the stochastic nature of the infection spreading process. For example, although Node 6 is only one link from the source, it can be infected by alternative nodes, such as Node 8. The cumulative effects posed by the full set of alternative paths to the same node can again yield unintuitive results regarding risk of infection. For instance, with no control implemented, the most likely path to Node 6 is Nodes 1 to 6, which has a likelihood (0.016) nearly four times the likelihood of the most likely path of 1–8–7 to Node 7 ($0.024 \times 0.145 = 0.00348$). However, at Time Step 5, Node 6 is only twice as likely to be infected as Node 7 if no control is implemented. This outcome reflects that the alternative paths to Node 7 cumulatively increase the probability of Node 7 being infected.

CASE STUDY

In addition to the demonstration network evaluated above, the model is applied to a real-world network defined by the U.S. domestic air traffic system. This case study considers the hypothetical scenario in which Ebola enters the United States through infected air travel passengers from one of the African countries where Ebola outbreaks are ongoing. The model is implemented to identify the U.S. states at highest risk of infection and where security and control resources should be implemented. Case data from the 2014 Ebola outbreak are used.

The analysis is conducted in two stages. First, a preprocessing step identifies the U.S. state with the highest importation risk. This location is then used as the hypothetical infection source in the second stage of the analysis, which includes implementation of the proposed bilevel model. The objective of the analysis is to determine the states where control resources should be allocated to minimize the total risk posed to the entire United States.

The first step of the analysis requires quantifying the risk posed to each U.S. airport connected via air travel from locations in Africa where an Ebola outbreak is known to have occurred in 2014. Therefore, the considered travel origin nodes are the major international airports in Guinea, Sierra Leone, and Liberia. The flight volumes (*22*) and reported number of infected patients in each region in Africa in October 2014 (*23*) are used to define the link transmission rates between airports with the equation presented previously, $\beta_{ij} = 1 - [1 - (k_i/h_i)]^{f_{ij}}$. The U.S. travel volumes from October 2011, which are supplied by the International Air Transport Association (*21*), are used as an estimate for the travel in October 2014, the peak period of the 2014 Ebola outbreak. The travel volumes are aggregated up to the country level for Africa and the state level for the United States; because there is only one major international airport that connects each infected African country to the United States, the aggregation provides a reasonable approximation for the outgoing risk posed by each region. The travel volumes are aggregated to the state level for the United States because of the computational complexity of the problem and the size of the U.S. air traffic network. The reliance on enumeration to generate upper-level solutions in this case study, coupled with the number of airports in the United States, would significantly increase the computational time and required resources. The outbreak size, k_i, is assumed to be the number of infected patients in each African country, which are all assigned to the largest international airport in the country. The origin population, h_i, for each African country is obtained from the World Bank online data repository (*24*). The aggregated flows between each African country, i, and each destination state in the United States, j, are computed as f_{ij} and are used to calculate β_{ij}. The total risk posed to each state j is the sum of the incoming risk from all origins i, $\sum_{i\in\gamma(j)} \beta_{ij}$. This analysis revealed New York to have the highest risk or greatest likelihood of an infected traveler entering one of the major airports from Africa. New York therefore was selected as the infection source for the second stage of analysis, which considers the scenario of an Ebola outbreak spreading within the United States through infected domestic air travelers.

For the second stage of the analysis, the structure and the transmission risks of the U.S. air traffic network are determined from flight travel data for October 2011 (*22*) and population data for the United States in 2014 (*25*). In this case study, only domestic air travel routes are considered. In this evaluation, each node in the network represents a state, and each link represents a travel route between two states. The bilevel model is then applied to the network. The following assumptions hold:

1. The transmission reduction factor is $\delta_i \in \{0.5, 1\}$ for all nodes $i \in M = N$.
2. The cost of control resource is $g_i(\delta_i) = 2(1 - \delta_i)$ for all nodes $i \in M = N$.
3. The budget of control resources is $B = 2$.
4. The time step at which the control strategy is assessed is $T = 5$.

The assumptions are similar to those used in the demonstration network, since relaxing these assumptions would increase the computational load significantly. Specifically, given the size of the case study problem, it is much harder to solve if $\delta_i \in [0, 1]$ or if $2 < B < N$. This topic will be addressed in future research. The performance of each strategy is again assessed with 100,000 lower-level simulation runs to achieve accuracy similar to that in the demonstration network. The definition of the time step is at the discretion of the modeler; in this study it is defined as a week. The time step unit of the travel data must match this defined time step so the model will be consistent. In this case study, only monthly data are available, and the weekly travel volumes are derived from dividing the monthly volumes. In future studies, week level data should be obtained to allow more accurate analyses.

In this model, the link transmission rates are calculated with the same expression as used in the demonstration network and the preprocessing step, and therefore β_{ij} generally is not equal to β_{ji} because of the nature of the actual travel volumes. Additionally, in this case study the outbreak size variable for each region is left constant at $k_i = 10$ for the duration of the model, as noted in the assumptions in mathematical formulation section.

The individual risk of infection for each state when no control is placed is presented in Table 3 (only the top 10 are shown), where how likely each state will be infected in a baseline situation is presented. In this instance, New York is the source node, so the risk level is 1. The effectiveness of the control strategies is shown in Table 4

TABLE 3 Risk to Each State If No Control Is Placed

Rank	State	State-Level Risk
1	New York (source)	1
2	Florida	0.43011
3	California	0.34672
4	Texas	0.22053
5	Illinois	0.19076
6	Georgia	0.15107
7	North Carolina	0.13002
8	Nevada	0.11258
9	Massachusetts	0.1054
10	Colorado	0.09452

(only the top 10 are shown) and is presented in the order of decreasing performance. The optimal control strategy is shown to be implementation of control in New York and Florida. New York is an expected choice of the model because it is the known source node. The performance of the strategies illustrates the counterintuitive results that can emerge because of the stochastic nature of epidemic dynamics. For example, Texas is the node with the fourth highest risk if no control measure was to be placed; its risk value is much greater than Nevada's, as shown in Table 3. However, as indicated in Table 4, Nevada is a better location to implement control than Texas. Examination of the data shows that the transmission rates β_{ij} from Nevada are almost always much higher than those from Texas. This result supports observations made on the demonstration network that nodes with more potential to spread the epidemic could be more important for targeting with control resources.

Certain simplifying assumptions were made in the model that could affect the outcomes and relative ranking. In this analysis, the outbreak size remains constant over time. Therefore, risk of spread is solely a function of the outgoing travel patterns and population. In reality, a region infected earlier in the outbreak could pose a greater risk over the course of the outbreak as the local number of cases increases. This region would also increase the risk posed to its set of highly connected regions. Thus, the assumed constant outbreak size for all infected states results in an underestimation of the risk values. This assumption will be relaxed in future research. Nonetheless, the resulting node infection probabilities at Time Step 5 (after 5 weeks) are fairly significant for some states, including Florida, California, and Texas, which reveals the potential harm posed by the large travel volumes between U.S. airports.

The assessment time step is arbitrarily set to $T = 5$ (5 weeks) for this analysis. However, it can be varied to reflect the policy maker's desired time frame. For example, for a faster-spreading outbreak, a shorter time frame would be desired. Additionally, only domestic travel links are considered in this study, which significantly reduces the size and complexity of the air traffic network. This reduction in network structure removes the international dimension of spreading risk, which is unrealistic. This assumption, along with state-level aggregation and limited set of considered strategies, is strictly related to the time and computational resources needed to solve the model with strict enumeration. With more efficient solution methods, a wider range of strategies and a more complete, spatially disaggregated network structure can easily be considered within this modeling framework. For example, with sufficiently detailed travel and infection data, the model can be applied to identify the best airports or routes to target within a region, at a daily time step increment. It can also be easily expanded to applications beyond the U.S. network.

CONCLUSIONS, LIMITATIONS, AND FUTURE RESEARCH

Understanding the role that the global air traffic network plays in the process of epidemic spreading is essential for the development of successful risk-mitigation strategies. The proposed model provides a framework for allocating control measures to at-risk regions in the event of an outbreak, when the available resources are limited.

A bilevel optimization model was proposed in which the upper-level model selects the optimal strategy and the lower-level problem simulates the epidemic dynamics. The objective of the model is to minimize the risk posed to the entire network. Because of the flexibility of the modeling framework, alternative objective functions can be considered—for example, minimizing the maximum risk to any region. A range of policy-based objectives will be explored in future research.

The model was applied in two case studies, a demonstration network and the U.S. domestic air traffic network. It was demonstrated

TABLE 4 Networkwide Risk for Strategies That Include New York

Rank	Control Strategy	Networkwide Risk of Strategy	Percentage Increase in Networkwide Risk (compared with optimal strategy risk)
1	{New York, Florida}	2.55093	0
2	{New York, District of Columbia}	2.58546	1.4
3	{New York, California}	2.5957	1.8
4	{New York, Illinois}	2.62001	2.7
5	{New York, Nevada}	2.62315	2.8
6	{New York, Missouri}	2.63238	3.2
7	{New York, Colorado}	2.63524	3.3
8	{New York, Georgia}	2.63611	3.3
9	{New York, North Carolina}	2.63634	3.3
10	{New York, Texas}	2.6365	3.4

that this model can provide insight into the dynamics of epidemic spread and can identify optimal strategies that may not be obvious from simple analyses of the network structure, by exploiting the heterogeneous nature of weighted air traffic network structures. This model is intended for use by decision makers who seek to develop optimized real-time control strategies in the event of an emerging infectious disease outbreak when effective vaccination or treatment is not yet available.

The main contribution of this paper is the proposed optimization framework. The work motivates additional research problems that could further improve the capabilities of this model. The optimization model does not consider the effects of the mobility and interaction dynamics of a local population and how the evolution of each local outbreak affects networkwide disease spread. The assumption that infected and noninfected individuals have the same probability to travel will be relaxed in future research, and the dynamic change in the local outbreak size will be incorporated. The solution method for the upper-level objective will be another focus of future research. In this study, exhaustive search was used to iterate over all feasible solutions. More efficient methods to be developed in the future will be applicable to large networks. This model can be expanded to applications beyond the U.S. network, at a much more disaggregate spatial (airports within a region) and temporal (daily) level, provided detailed data are available.

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