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Decision-support tools for influenza pandemic preparedness

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Contents

An introduction to influenza

Influenza pandemics

- Influenza pandemics include: 1918, 1957, 1968, and 2009
- 50 million deaths globally in 1918; 284,000 in 2009 H1N1
- Threats of H5N1 and H7N9 are emerging

An introduction to influenza

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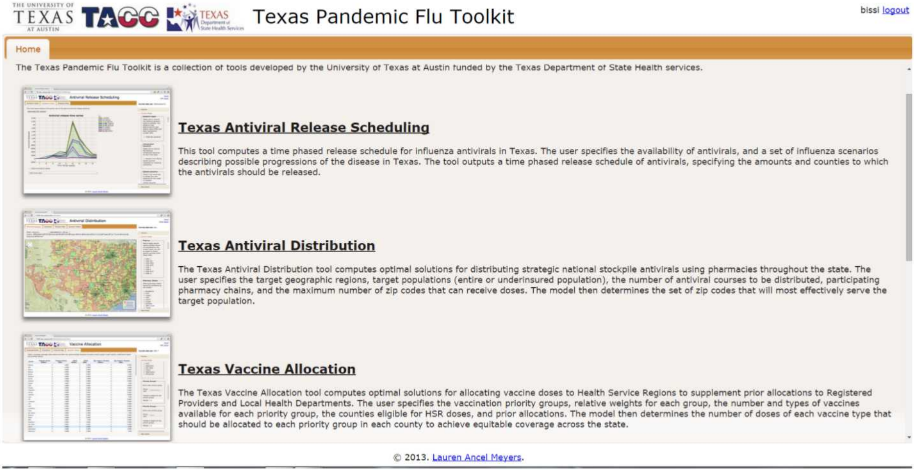
Control measures

- Vaccines: most effective, but development may take months
- Antivirals: reduce symptoms and transmission, particularly important prior to vaccines
- Other non-pharmaceutical interventions

Web-based decision support tools built for Texas DSHS



http://flu.tacc.utexas.edu/

Contents

Tool 1: Antiviral distribution

Bismark Singh, Hsin-Chan Huang, David P Morton, Gregory P Johnson, Alexander Gutfraind, Alison P Galvani, Bruce Clements, and Lauren A Meyers. *Optimizing Distribution of Pandemic Influenza Antiviral Drugs*. Emerging Infectious Diseases, 21(2):251, 2015.

Key questions:

- How far would people travel to obtain antivirals?
- Which pharmacies to use for distribution?
- How to handle disparities between "smaller" and "larger" ZIP codes?

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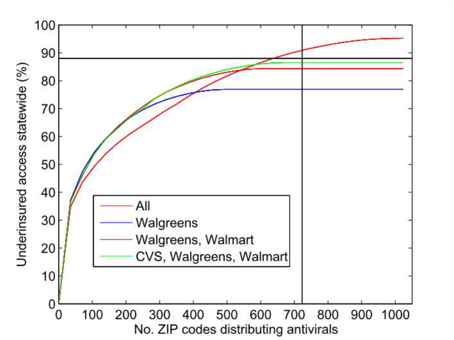
Models:

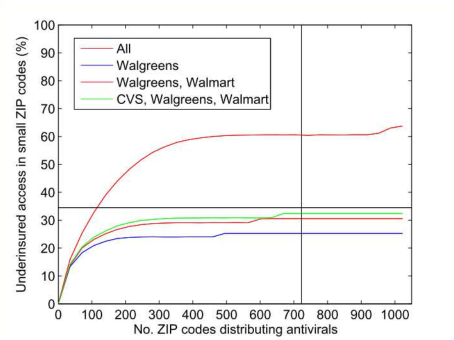
- *Willingness-to-travel model*: Exponentially decaying model fit to National Household Travel Survey data
- *Optimization model*: Facility location model to maximize access to the "target" population

Result 1: Texas achieved high access statewide, but low access in small ZIP codes in 2009 H1N1

Statewide



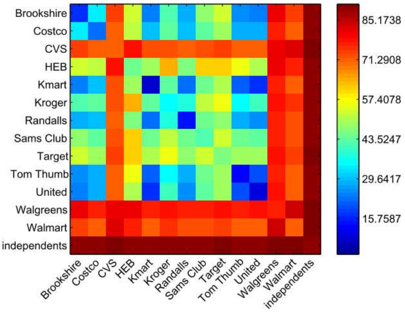
Small ZIP codes



Vertical, horizontal lines: number of ZIP codes in Texas 2009 distribution network, estimated access achieved.

Result 2: Major chains provide high access statewide, but low access in small ZIP codes in 2009 H1N1

Statewide



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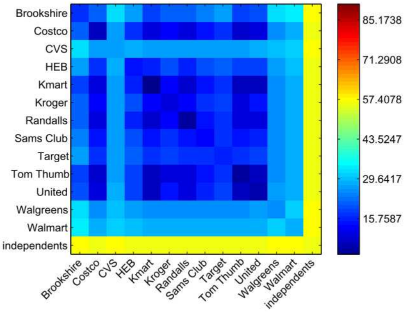

Contents

Tool 2: Vaccine allocation

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Key considerations:

- Provide majority of doses to healthcare providers based on requests
- Optimize small reserve of doses to achieve "proportionally fair coverage" across priority groups & geographic regions
- Keep the policy "simple" & maintain regional equity

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Vaccine Allocation:

8.68M vaccines received by Texas as of August 3, 2010

- Pull-based: 93.2% via healthcare providers and state health offices
- Push-based: 6.8% through health service regions (HSRs)

$$\text{Ideal ratio} = 1 - \frac{\text{vaccines doses received in HSR counties}}{\text{number of priority individuals in HSR counties}} = 0.389$$

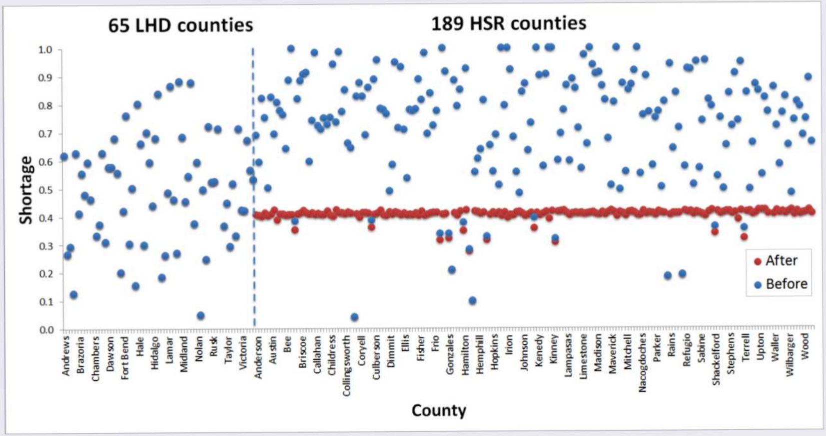
Tool 2: Vaccine allocation

Models:

- *Convex quadratic program*: Theorem ensures optimal shortages of two county-priority group pairs are inversely proportional to weights if final shortages are positive
- *Secondary optimization models*: (i) Minimize vaccine types provided to a priority group, and (ii) assign similar vaccine types across different geographic regions

Result 1: Proportional fairness brings total shortage in almost all served counties to at most the ideal ratio

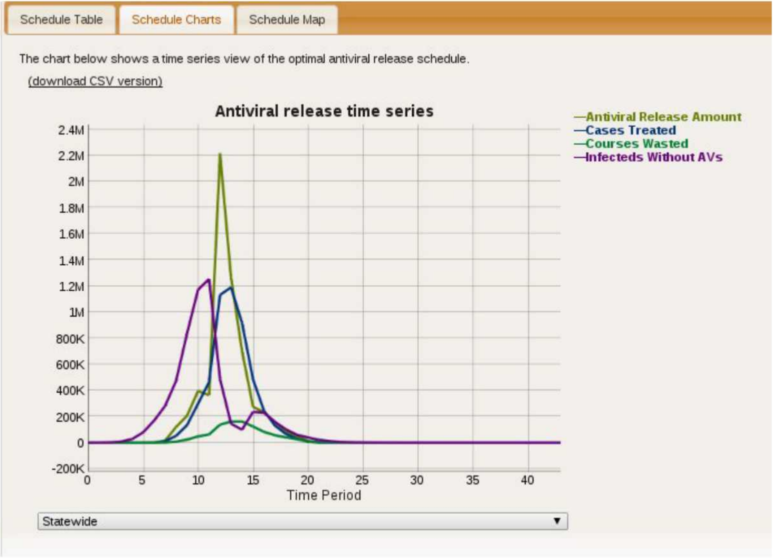
Shortage before and after entire modeling process



Only a subset of the county names are displayed

Contents

Tool 3: Antiviral Release Scheduling



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Topic 3: Antiviral release scheduling

Key considerations:

- Disease evolution is highly stochastic
- How many antivirals to release spatiotemporally when only limited information on disease is initially available?

Optimization model

A two stage stochastic program with binaries in second stage

max	$\mathbb{E}$[Benefit]
s.t.	Release antivirals less than available
	Carry antivirals that were not picked up to next time stage
	Pick up all antivirals that can be picked up

Decision variables: # Antivirals to release: 1st stage; # excess antivirals: 2nd stage; # antivirals that get picked up: 2nd stage.

Some theoretical results

- The model has relatively complete recourse

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Some theoretical results

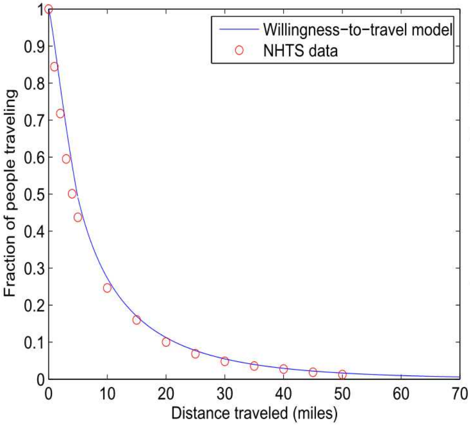
- The model has relatively complete recourse
- LP relaxation can be far from optimal. Why?
- Averaging the uncertainty can also result in an optimal solution far from optimal

Currently working on...

- Currently the model is intractable even for just 2 scenarios (33K binaries)
- Studying a Lagrangian relaxation
- Study theoretical hardness of the model

Contents

Willingness-to-travel model



Using NHTS data for both entire U.S. population and U.S. underinsured population

$$\hat{P}_{at\_risk}(d) = \begin{cases} \exp(-0.1022 d^{1.21}), \\ \text{if } d < 5\text{miles} \\ 1.529 \exp(-0.433 d^{0.60}), \\ \text{if } d \geq 5\text{miles.} \end{cases}$$

Antiviral Distribution: Optimization model

Indices and sets:

$i \in I$	locations of customers [ZIP codes]
$j \in J$	ZIP codes containing candidate pharmacies that can be selected

Data:

pop_i	target population of customers in ZIP code i
p_{ij}	fraction of target population in ZIP code i willing to go to ZIP code j to obtain an antiviral
b	bound on number of ZIP codes selected

Decision variables

x_j	1 if we select a pharmacy in ZIP code j; else 0
y_{ij}	1 if ZIP code j contains ZIP code i's most accessible pharmacy; else 0

Formulation

$$
\begin{aligned}
z^* = \max_{x,y} \quad & \sum_{i \in I} \sum_{j \in J} pop_i \, p_{ij} \, y_{ij} \\
\text{s.t.} \quad & \sum_{j \in J} x_j \leq b \\
& \sum_{j \in J} y_{ij} = 1, \forall i \in I \\
& y_{ij} \leq x_j, \forall i \in I, j \in J \\
& x_j, y_{ij} \in \{0, 1\}, \forall i \in I, j \in J.
\end{aligned}
$$

Optimization model

Indices and Sets

$i \in I$	counties
$j \in J$	priority groups
$k \in K$	vaccine types
K_j	$= \{ \; k \in K$: vaccine types for which priority group j is eligible $\}$
L	$= \{ \; (i,j) \in I \times J : n_{ij} > 0$ and $f_{ij} < 1 \; \}$
G	$= \{ \; (i,j,k) \in I \times J \times K : (i,j) \in L$ and $k \in K_j \; \}$

Data

m_{ijk}	doses of vaccine type k previously allocated to county i for priority group j
n_{ij}	population of county-priority group pair (i,j)
w_{ij}	weight of county-priority group pair (i,j); $w_{ij} \geq 1$
b_k	available discretionary doses of vaccine type k
f_{ij}	coverage to date for pair (i,j); i.e., $\frac{\sum_{k \in K_j} m_{ijk}}{n_{ij}}$

Optimization model (contd.)

Decision Variables

Q_{ijk} available HSR doses of type k allocated to priority group j in county i

Formulation

$$\min_{Q} \quad \sum_{(i,j)\in L} w_{ij} n_{ij} \left[1 - \left(f_{ij} + \frac{\sum_{k\in K_j} Q_{ijk}}{n_{ij}}\right)\right]^2 \tag{2a}$$

$$\text{s.t.} \quad \sum_{(i,j):(i,j,k)\in G} Q_{ijk} \leq b_k, \forall k \in K \tag{2b}$$

$$f_{ij} + \frac{\sum_{k\in K_j} Q_{ijk}}{n_{ij}} \leq 1, \forall (i,j) \in L \tag{2c}$$

$$Q_{ijk} \geq 0, \forall (i,j,k) \in G \tag{2d}$$

Output

Q^*_{ijk} optimal allocation

s_{ij} optimal final shortage of (i,j) pair; i.e., $1 - (f_{ij} + \frac{\sum_{k\in K_j} Q^*_{ijk}}{n_{ij}})$

Proportional-fairness theorem

Theorem

By using model (2) to allocate available discretionary vaccine doses, the optimal shortage of two county-priority group pairs, (i, j) and (i', j'), denoted s_{ij} and $s_{i'j'}$, are inversely proportional to their weights, w_{ij} and $w_{i'j'}$, if
(i) both s_{ij} and $s_{i'j'}$ are greater than 0;
and,
(ii) (i, j) and (i', j') have a common type of available discretionary vaccine allocated in an optimal solution.

Proof: ▸ Proof

Based on KKT conditions for the optimization model.

Proportional-fairness theorem

Theorem

By using model (2) to allocate available discretionary vaccine doses, the optimal shortfalls of two county-priority group pairs, (i,j) and (i',j'), denoted g_{ij} and $g_{i'j'}$, are inversely proportional to their weights, w_{ij} and $w_{i'j'}$, if
(i) both g_{ij} and $g_{i'j'}$ are less than 1;
and,
(ii) (i,j) and (i',j') have a common type of available discretionary vaccine allocated in an optimal solution.

Proof

Let λ_k and ν_{ij} be the Lagrange multipliers of constraints (2b) and (2c), respectively. Let $F(Q)$ denote the objective function in (2a). Then,

$$\frac{\partial F}{\partial Q_{ijk}} = 2\,w_{ij}\left[-1 + \left(f_{ij} + \frac{\sum_{k\in K_j} Q_{ijk}}{n_{ij}}\right)\right].$$

Proof (contd.)

Karush-Kuhn-Tucker optimality conditions for the convex quadratic program are:
Primal feasibility, or constraints (2b), (2c), and (2d)
Dual feasibility and the complementary slackness conditions:

$$\lambda_k^* + \frac{\nu_{ij}^*}{n_{ij}} \geq 2\, w_{ij} \left[1 - \left(f_{ij} + \frac{\sum_{k \in K_j} Q_{ijk}^*}{n_{ij}} \right) \right], \forall (i,j,k) \in G$$

$$\lambda_k^* \geq 0, \forall k \in K, \nu_{ij}^* \geq 0, \forall (i,j) \in L$$

$$\lambda_k^* \left(b_k - \sum_{(i,j):(i,j,k) \in G} Q_{ijk}^* \right) = 0, \forall k \in K$$

$$\nu_{ij}^* \left[1 - \left(f_{ij} + \frac{\sum_{k \in K_j} Q_{ijk}^*}{n_{ij}} \right) \right] = 0, \forall (i,j) \in L \qquad (*)$$

$$Q_{ijk}^* \left\{ \lambda_k^* + \frac{\nu_{ij}^*}{n_{ij}} - 2\, w_{ij} \left[1 - \left(f_{ij} + \frac{\sum_{k \in K_j} Q_{ijk}^*}{n_{ij}} \right) \right] \right\} = 0, \forall (i,j,k) \in G \quad (**).$$

Proof (contd.)

Consider two (i, j) and (i', j') pairs that satisfy hypotheses (i) and (ii).

Hypothesis (i) & complementary slackness condition (*) $\Rightarrow \nu^*_{ij} = \nu^*_{i'j'} = 0$.
Hypothesis (ii) $\Rightarrow Q^*_{ijk} > 0$ and $Q^*_{i'j'k} > 0$ for some k and hence by (**) for that k:

$$\lambda^*_k = 2\, w_{ij} \left[1 - \left(f_{ij} + \frac{\sum_{k \in K_j} Q^*_{ijk}}{n_{ij}} \right) \right] = 2\, w_{i'j'} \left[1 - \left(f_{i'j'} + \frac{\sum_{k \in K_j} Q^*_{i'j'k}}{n_{i'j'}} \right) \right].$$

$\Rightarrow$

$$\frac{s_{ij}}{s_{i',j'}} = \frac{w_{i'j'}}{w_{ij}}.$$

Thus, under hypotheses (i) and (ii) the shortfalls are inversely proportional to the weights.

■

Result 2: Fewer vaccine types are assigned to a priority group after secondary optimizations

Percentage of doses assigned to each priority group

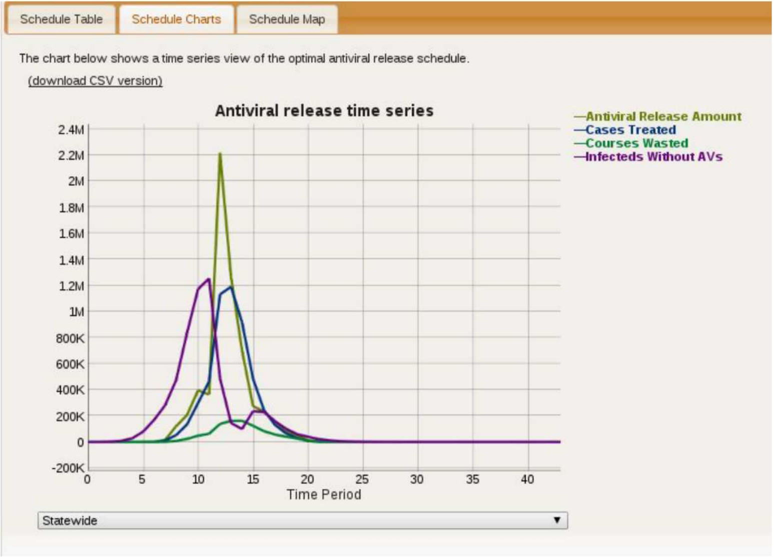
(%)	Before secondary optimizations				After secondary optimizations			
	PFS baby	PFS	MDV	LAIV	PFS baby	PFS	MDV	LAIV
0-3 years	100	0	0	0	100	0	0	0
4-24 years	0	12.6	55.7	31.7	0	0	73.3	26.7
25-64 years (HR)	0	22.8	77.2	0	0	45.2	54.8	0
Pregnant women	0	44.2	55.8	0	0	100	0	0
Infant caregivers	0	28.2	37.2	34.6	0	0	0	100

Result 3: Variability of solutions across regions decreases after secondary optimizations

Percentage of doses assigned to each HSR

(%)	Before secondary optimizations				After secondary optimizations			
	PFS baby	PFS	MDV	LAIV	PFS baby	PFS	MDV	LAIV
HSR 1	3.5	26.3	46.2	24.0	3.5	14.8	58.7	23.0
HSR 2/3	2.8	12.8	66.3	18.1	2.8	16.1	60.6	20.5
HSR 4/5N	2.8	18.9	57.2	21.1	2.7	19.0	61.3	17.0
HSR 6/5S	3.0	13.8	62.2	21.0	3.0	15.1	61.1	20.7
HSR 7	2.9	16.6	60.2	20.3	2.8	15.7	61.8	19.6
HSR 8	3.1	16.8	61.1	19.0	3.1	19.3	57.1	20.5
HSR 9/10	3.3	31.1	44.2	21.4	3.5	19.3	58.8	18.4
HSR 11	4.3	21.3	52.9	21.5	4.3	19.8	53.9	22.0

Antiviral release scheduling tool built for Texas DSHS



Parameter estimation

- Define: benefit of antivirals in averting the death of a member of a population group, g, as,
$$b_g = \underbrace{\mathbb{P}(\text{death}|\text{without antivirals})_g}_{\text{case fatality rate}} - \underbrace{\mathbb{P}(\text{death}|\text{with antivirals})_g}_{\text{derived from mortality odds ratio}}$$

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- Define: $B^{\omega}_{c,t}$ as population weighted average of b_g of providing antivirals to the infected and the *worried-well* for all scenario, county, time
- $u^{\omega}_{c,t,g}$ obtained from an epidemic simulator

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- This benefit can be negative!

Contents

Acknowledgements

Sandia National Laboratories

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