Uncertainty Analysis of Pandemic Influenza

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with
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Influenza Modeling Applications

• Planning for Pandemic (H5N1) 2006-2007 and and Provided Decision Support for (H1N1) 2009
  – Projected timing and potential impacts of H5N1
  – Estimated impacts of pharmaceutical and non-pharmaceutical interventions for H1N1

• Used by the Modeling of Infectious Disease Agent Study (MIDAS)
  – Used for cross-model comparison of CDC adopted strategies

H1N1 Phase I Study
H5N1 Study
H1N1 Phase II Study
Perspective of Various Epidemiological Models

Spatial Scale

- **High** (individual, minute-by-minute)
- **Moderate** (community, day and night)
- **Low** (population stratified by age)
  (homogeneously mixed population)

Computational Cost

- **Supercomputer**
- **Workstation/PC**

Key Resources

- Chemical Industry
- Agriculture
- Fuel Services
- Government
- Defense Ind. Base
- Postal/Shipping
- Public Health
- Electric Power
- Banking/Finance
- Government

Economic Products

- Water
- Telecommunications
- Transportation
- Emergency Services
- Government Regulation

Epidemiological Models

- **EpiSimS**
- **EpiCast**
- **CIPDSS**
- **GlobalCURE**
Critical Infrastructure Protection – Decision Support System (CIPDSS)

- Decision support system created to assist leaders to:
  - Prioritize protection
  - Mitigation
  - Response

- Develop methodologies for analysis of alternatives
- Intended to support investment decisions in infrastructure protection and grants programs
Critical Infrastructure Protection – Decision Support System (CIPDSS)

Scenario-Driven Analyses

Interdependent Infrastructure Models

Broad threat representation enables risk-informed decision making

17 critical infrastructures; National/regional and metropolitan scale

Decision Model to Evaluate Trade-Offs

Quantify/Visualize Consequences

Compare protective measures; Support risk reduction investment decisions

“Order-of-magnitude” estimates; uncertainty analysis; sensitivity analysis; screening studies
• National Model
  – National scale infrastructures

• Metropolitan Model
  – City scale infrastructures

• Decision Model
  – Risk attitude
  – Preferred alternatives
Disease Model Linkage to Healthcare

- General Infectious Disease (GID) outputs of symptomatic people flow into the Healthcare model

### Flow of symptomatics

- Start
  - Self-care: 40%
  - Medical Care: 60%
- Physician's Office: 30%
- Emergency Care: 75%
- EMS: 25%
- ER: 75%
- Hospital: ~85%
- Recover: ~70%
- Die: ~0.08%
- die: ~50%
- die: ~1%

### Healthcare backlogs

- Baseline
- Fear-Based Self-Isolation
- Idealized TLC
- TLC Lite
- Antiviral
- Partially Effective Vaccine
- Anticipated Intervention

* Death fractions are variable, depending on calculation in epidemiological model.
Model Outputs

- **Health and Human Safety**
  - Deaths, illnesses
  - Number hospitalized

- **Economic**
  - Economic loss (lost Gross Domestic Product)

- **Other**
  - Attack rate
  - Peak absenteeism
  - Duration of pandemic
  - Effect on infrastructure operations
Two Phase Analysis

- Department of Homeland Security-Office of Health Assurance
  - What are the impacts of pandemic influenza?

- Phase 1 – analysis of specified mitigation scenarios to quantify key outputs, assuming a 1918-like pandemic

- Phase 2 – estimating distributions of pandemic consequences given uncertainties about
  - health policies
  - disease manifestation
  - social response
  - infrastructure response
Epidemiological Modeling

- **CIPDSS** – SEIR systems dynamics model
  Age- and occupation-related compartments

- **EpiSimS** – agent-based network model
  Synthetic Population – 19 million agents
  6 million households

- **Loki-Infect** – agent-based network model
  10,000 agent community
CIPDSS Model Comparison to EpiSimS

- **EpiSimS**
  - An agent-based, high resolution model based on Census data and mobility patterns

- **CIPDSS**
  - Compartmental model
    - Susceptible, exposed, infected, recovered (SEIR)
Key Modeling Assumptions

Social Distancing could be:
- fear-based quarantine
- school closures
- one parent staying home
- telecommuting

Mitigations based on recommended community and national pandemic influenza plans

The regional population and travel model tracks the healthy and afflicted populations and calculates how many contagious people are currently visiting another region.
Sources of Uncertainty

• Biological
  – Vaccine and antiviral effectiveness
  – Disease reproductive number, fatality rate, duration of disease stages
  – Infectiveness prior to clear symptoms
  – Number and relative infectivity of asymptomatics

• Policy-based resources
  – Initial stockpiles of antivirals and pre-pandemic vaccine

• Sociological response
  – Fraction of people seeking healthcare
  – Absenteeism response to the disease
  – Degree of social distancing

• Infrastructure response
  – Public health policy for capacity-limited healthcare operations
## Transmission Parameters Varied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Contacts Per Case</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Reproductive Number (All Ages)</td>
<td>1.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Fraction of Transmission Prior to Clear Symptoms</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Relative Contagion of Asymptomatics</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Fraction of Asymptomatic</td>
<td>0.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Public Health Parameters Varied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Mortality Enhancement Multiplier</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Base Fraction of Affected Seeking Health Care</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Detection Threshold</td>
<td>1</td>
<td>512</td>
</tr>
</tbody>
</table>
Evaluation of Public Health Interventions

• Vaccination
  – Use of a pre-pandemic, unmatched vaccine
  – Use of matched vaccine after development delay
  – Mass vaccination vs. targeted vaccination

• Antivirals
  – therapeutic
  – prophylaxis

• Isolation/Quarantine

• Social Distancing

• Interventions evaluated in the context of uncertainty about the disease and society’s response to the pandemic
### Vaccine and Antiviral Parameters Varied

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial antiviral availability</td>
<td>21M</td>
<td>80M</td>
</tr>
<tr>
<td>Antiviral Standard Production Rate</td>
<td>0</td>
<td>120M</td>
</tr>
<tr>
<td>Fraction Antivirals Applied to Prophylaxis</td>
<td>0.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Death Rate Reduction From Antivirals</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Initial Vaccine Stockpile (Partially Effective)</td>
<td>21M</td>
<td>121M</td>
</tr>
<tr>
<td>Vaccine Effectiveness (Partially Effective)</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Vaccine Effectiveness (Fully Effective)</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Time Before Vaccine Gives Immunity (Both Types)</td>
<td>168</td>
<td>1152</td>
</tr>
</tbody>
</table>
# Influenza Characteristics

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>Varied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Fatality Rate (All population groups)</td>
<td>0.01 - 0.15</td>
</tr>
</tbody>
</table>

**Disease Stage Time Periods**

- Time to Incubate: 12 - 96 days
- Duration of Prodromal (infectious/asymptomatic): 12 - 96 days
- Duration of Early Symptoms: 24 - 120 days
- Time to Recover: 120 - 552 days
Phase 1 Key Results

- Impacts to the health care system are a major concern
- Workforce reductions are a concern in some infrastructures
  - safety limitations on working hours for key operation personnel
  - specialized training requirements and logistical/scheduling limitations
- Economic impacts
  - Short-term $85B to $130B; driven by absenteeism
  - Long-term $270B to $740B; driven by fatalities
Organization of Phase 2 Results

• Public health intervention strategies under uncertainty in
  – Disease manifestation
  – Effectiveness and availability of pharmaceutical interventions
  – Compliance and behavioral response
  – Public health infrastructure resilience

• Multi-attribute value risk assessment of health intervention strategies
  – Antivirals
  – Social distancing
  – Partially effective early (pre-pandemic) vaccines
  – Fully effective vaccines
Mitigation measures model inputs considered in the sensitivity analysis

- Initial antiviral stockpile and production rate
- Fraction of antivirals applied to prophylaxis
- Death rate reduction from antivirals
- Vaccine production rate (weekly) and initial stockpile
- Vaccine effectiveness
- Fraction of day masks are worn, % population wearing them, and transmissivity
- Rate of social distancing or self-quarantine
Sensitivity Analysis Concerns

• Some range bounds set at high levels
  – Some variables do not appear as sensitive, even though intuitively they should, i.e., Vaccine efficacy

• Narrow uncertainty ranges (optimistic assumptions)
  – Vaccine efficacy
  – Anti-viral effectiveness (resistant strains exist)
  – $R_0$ and case mortality rate could vary over larger range
  – New mask transmissivity

• Some uncertainties omitted
  – Vaccination rate / willingness of population to get vaccine
Sensitivity Analysis

- Objective: reduce input parameters to those that contribute significantly to output variance
- 32 of ~100 parameters selected for sensitivity analysis
- Typically use uniform distribution
- 20 of 32 retained for uncertainty analysis
- Remaining inputs set at constant values

Most Sensitive Inputs Include:

- Reproductive Number ($R_0$)
- Proportion of Transmission Occurring Prior to Symptoms
- Time to Recover
- Fraction of Infected People that are Asymptomatic
- Relative Contagion of Asymptomatics

\[ R^2 = \frac{\text{Var}(E[y|x_i])}{\text{Var}(y)} \]

R^2 (0 to 0.78) - PIPHII07Feb15.1: Runs 64 30 Inps PI - base
Uncertainty Analysis

• Objective: derive empirical distributions for key output measures

• Approach
  – Designed computer experiment
  – 20 factor 512 run Latin hypercube sample
  – Selected distributions for input parameters
  – 24 mitigation strategies

• Results
  – 243 outcomes per strategy
  – Assessment of expected utility of each strategy

\[ y = M(x) \]

Perturbation in \( x \) causes perturbation in \( y \).

\(^1\)Results rejected if \( R_o < 1 \)
Outcome Distributions

- **Observed Attack Rate**
  - no intervention (vaccination strategy 1)

**Model**

- **R₀**
  - Gamma

- **Time to Recover**
  - LogNormal

- **Fatality Rate**
  - Beta

- **Social Distancing**
  - No Social Distancing

**Graph**

- Observed Attack Rate
- no intervention
- (vaccination strategy 1)
Insights from Uncertainty Analysis

- Generate plausible disease scenarios
  - Assume independent inputs
- Estimate range of pandemic consequences
  - Response to mitigation strategies

Potential for extreme consequences

Assumes social distancing and use of antivirals
• High variability due to uncertainty in inputs
• Vaccination strategies
  1. No vaccination or contact tracing
  2. Contact tracing without vaccination
  3. Mass vaccination only with no early vaccine
  4. Mass vaccination with early vaccination
  5. Targeted followed by mass vaccination with early vaccination
  6. Targeted vaccination with early vaccination
• On/off antivirals
• On/off social distancing

Shaded boxes show the interquartile range\(^1\) (IQR)
Horizontal bar in box is median
Circle with “+” depicts average
Whisker extends to min(max value, 1.5 * IQR)

\(^1\) IQR is the distance between the third and first quartiles and is a nonparametric measure of variability.
Variability in Model Results

Peak Fraction Workers Unavailable

- Variability due to uncertainty in inputs
- Observations
  - No Social Distancing provides lower average levels of worker absenteeism
  - Social Distancing roughly doubles the average absenteeism rate
  - Strategy 4 (Mass vaccination with early vaccination) provides approximately 25% reduction in mean absenteeism compared to other strategies
  - In less than 10% of cases, absenteeism can exceed 30%

Shaded boxes show the interquartile range\(^1\) (IQR)
Horizontal bar in box is median
Circle with “+” depicts average
Whisker extends to min(max value, 1.5 * IQR)

\(^1\) IQR is the distance between the third and first quartiles.
Evaluation of Intervention Strategies

- All interventions provide reduction in deaths relative to base case
  - Antivirals provide minor benefit
  - Social distancing gives big benefit, but costly
  - Vaccination method (mass or targeted) matters less than effectiveness of vaccine

**Best strategy** is SDAV4:
- Mass vaccination with pre-pandemic vaccine followed by mass vaccination with strain-specific vaccine, with social distancing and antivirals

# Strategy
1. No vaccination or contact tracing
2. Contact tracing without vaccination
3. Mass vaccination only with no early vaccine
4. Mass vaccination with early vaccination
5. Targeted followed by mass vaccination with early vaccination
6. Targeted vaccination with early vaccination
Economic Cost

- All interventions have an effect on the economy
- Primary mechanism is lost worker productivity due to absence from work
- Note that social distancing imposes a greater economic cost
- Antivirals tend to reduce economic loss

**Best strategy** with respect to this metric is noSDAV4: mass vaccination with pre-pandemic vaccine followed by mass vaccination with strain-specific vaccine, using antivirals but no social distancing

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<table>
<thead>
<tr>
<th>Vaccination Strategy</th>
<th>Percent GDP Lost over 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No vacc or contact tracing</td>
<td>0%</td>
</tr>
<tr>
<td>2. CT w/o vacc</td>
<td>1%</td>
</tr>
<tr>
<td>3. Mass vacc, no early vacc</td>
<td>2%</td>
</tr>
<tr>
<td>4. Mass vacc w/ early vacc</td>
<td>3%</td>
</tr>
<tr>
<td>5. Target/mass vacc w/ early vacc</td>
<td>4%</td>
</tr>
<tr>
<td>6. Targeted vacc w/ early vacc</td>
<td>5%</td>
</tr>
</tbody>
</table>

SD = social distancing
AV = antivirals
Variability in Results

- High variability due to uncertainty in inputs
- 24 mitigation strategies
  - On/off antivirals (AV)
  - On/off social distance (SD)
  - 6 combinations of vaccination and contact tracing
- Even the best mitigation strategy has a wide range of outcomes, up to 16 million deaths, although its mean value is 1.2 million

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Deaths (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>noSDnoAV</td>
<td>0</td>
</tr>
<tr>
<td>noSDAV</td>
<td>1</td>
</tr>
<tr>
<td>SDnoAV</td>
<td>2</td>
</tr>
<tr>
<td>SDAV</td>
<td>3</td>
</tr>
</tbody>
</table>

Shaded boxes show the interquartile range\(^1\) (IQR)
Horizontal bar in box is median
Circle with “+” depicts average value
Whisker extends to min(max value, 1.5 * IQR)

\(^1\) IQR is the distance that spans the middle 50 percent of the data.
Comparison to 1918-like Pandemic

- Pre-pandemic planning and preparation
  - 1918-like pandemic is close to average of best strategy
  - 90th percentile outcomes using best strategy – twice as severe as 1918 pandemic

![Estimated Probability Distributions](image)

No Mitigation vs. Best Strategy

<table>
<thead>
<tr>
<th>Fatalities (millions)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>0.1</td>
<td>0.40</td>
</tr>
<tr>
<td>0.2</td>
<td>0.36</td>
</tr>
<tr>
<td>0.3</td>
<td>0.32</td>
</tr>
<tr>
<td>0.4</td>
<td>0.28</td>
</tr>
<tr>
<td>0.5</td>
<td>0.24</td>
</tr>
<tr>
<td>0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>0.7</td>
<td>0.16</td>
</tr>
<tr>
<td>0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>0.9</td>
<td>0.08</td>
</tr>
<tr>
<td>1.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Fatalities for 1918-like Pandemic ≈ 1.5M
Overall Cases vs. 12 mitigation efficacy parameters

- Weekly Vaccine Production Rate
- Rate of Self-Quarantine
Pandemic Influenza Policy Analysis

- Uncertainty in disease characteristics dominates other uncertainties with respect to the
  - Potential illnesses
  - Deaths
- Effective intervention strategies greatly reduce the risks and uncertainties in outcomes
  - Illnesses
  - Deaths
  - Long-term economic impacts

No intervention

Mass Vaccination
Social Distancing
Antiviral Treatment
Conclusions

• High variability in outcomes of pandemic influenza
  – Primarily due to uncertainty in biological factors
  – Substantial likelihood of severe pandemic consequences

• Delay pandemic effects
  – Use preplanned stockpiles until strain-specific vaccines ready
  – Use multiple strategies: social distancing, pre-pandemic vaccine and antivirals

• Effective interventions
  – Social distancing is costly but effective
  – Pre-pandemic vaccine is not guaranteed to be effective
  – Antivirals are relatively inexpensive, may not be effective, but must be plentiful

• Minimize expected combined equivalent cost using a robust mixed strategy such as SDAV4
  – use of pre-pandemic vaccine followed by mass vaccination with social distancing and antivirals
Host Heterogeneity

- Within a population there will be great variation between individuals for their response to an infectious disease and impact transmission.
- Superspreaders are through contact rates, viral shedding rates, and disease duration.
- Future studies on emerging influenzas should include host heterogeneity.
We thank the U.S. Department of Homeland Security Office of Health Affairs for funding and the EpiSimS working group at Los Alamos National Laboratory for input and comparison. We are grateful to Perry Klare for model development and we thank B. McMahon expertise and comments. Sara Del Valle was the Principle Investigator for the H1N1 Pandemic Influenza Study.