May 2015

Preliminary Evaluation of the Disease Surveillance System During Influenza Outbreaks of Pandemic Scale

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**Recommended Citation**

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Abstract
In the United States it is currently unknown whether the influenza surveillance system is capable of producing timely and accurate data for case estimation during an outbreak of pandemic scale. This simulation provides a preliminary evaluation of the surveillance system's ability to collect data and produce timely and accurate trends of cases confirmed with an influenza virus. For the evaluation, a computer-based simulation of the data-collection process was used, which was validated with real demographic and epidemiologic information. The results were analyzed to determine the most significant behavioral and operational factors influencing the data collection and to propose the exploration of more efficient data-collection policies for the generation of timely and accurate trends of confirmed cases.

Keywords
Influenza simulation, influenza surveillance, influenza data collection

Cover Page Footnote
We thank Dr. Lillian Stark, retired virologist from the Florida Department of Health, and Dr. Susan Peters, former epidemiologist from the Michigan Department of Community Health for discussing with us about the operations of state viral surveillance laboratories. No competing financial or editorial interests were reported by the authors of this paper.
INTRODUCTION

Pandemic influenza (PI) outbreaks are unpredictable and potentially devastating public health issues. This unpredictable behavior necessitates proper outbreak management as the disease progresses. In the U.S., one of the most important information sources comes from data collected by the state viral surveillance labs (VSL). This information is in turn reported to Centers for Disease Control and Prevention, which aggregates other reports of confirmed cases to present a final daily number per state and to estimate pandemic trends.

During a pandemic influenza outbreak, the capacity of the VSL is generally exceeded due to the high demand of testing services, which are offered for free. This tendency forces the VSL to restrict the arrival of specimens from healthcare providers, based on operational factors of the surveillance system. The effect of these operational factors, along with other behavioral factors of the population could result in a distorted view of the outbreak’s epidemiologic features, a delay in accurate information, and unnecessary costs.

A screening experiment was performed to explore the effect of different factors in the disease predictive error of a trend of confirmed cases, using an agent-based simulation of disease spread.

AGENT-BASED SIMULATION

The sampling and testing of specimens were simulated in an urban population. This model is developed on top of an existing agent-based model that simulates the spread of a pandemic influenza H1N1 virus, and one of its seasonal antigenic variants (SI). Both viruses are seeded in a population that considers schools, workplaces, and errand places. The simulation was populated using information from the Hillsborough County in Tampa, Florida. The data collected for the simulation were obtained from the 2002 U.S. Economic Census, the 2001 American Community Survey, and the 2001 National Household Travel Survey. For a population of 1,000,000, a total of 12,800 businesses and 500,000 households were simulated.

The underlying influenza spread model described in Prieto and Das 2014 was used. Under this model, and in the absence of containment measures, an infected individual contacts a susceptible according to the following probabilities:

\[ p_{i,h,PI}^s = \frac{R_{PI}^s}{(1-\gamma)\pi_s + \gamma} w^s(t) \quad \text{and} \quad p_{i,h,PI}^a = \frac{\gamma R_{PI}^a}{(1-\gamma)\pi_s + \gamma} w^a(t) \]

Where

\[ p_{i,h,PI}^s \quad \text{and} \quad p_{i,h,PI}^a \] are the probabilities that a susceptible individual is infected at her household at time \( t \) by either a symptomatic (\( s \) ), or an asymptomatic (\( a \) ) PI individual.

\( R_{PI}^s \) is the number of infected PI cases that are created by an already infected case. Note that a similar set of equations exist for SI (\( p_{i,h,SI}^s, p_{i,h,SI}^a \)). Values of \( R_{PI}^s = 1.8 \), and \( R_{SI}^s = 1.3 \) were used as the reproduction numbers for the PI and the seasonal influenza viruses, respectively.
$w^r(t)$ and $w^o(t)$ are the infectiousness profiles of an individual depending on her symptomatic status. The $w^r(t)$ of the H1N1 was used for both viruses and was extracted from empirical studies on the viral shedding of symptomatic volunteers\(^2\) (Figure 1 is an example of $w^r(t)$).

$c_{i,h}$, $c_{i,w}$, and $c_{i,o}$ are the number of contacts made by the infectious case during a day in her household ($h$), workplace ($w$), or other errand places ($o$). These contacts are generated by the simulation model.\(^2\) The factors $\kappa^h$, $\kappa^w$, and $\kappa^o$ account for closeness and duration of contacts.

$\pi_s$ is the probability of an infected being symptomatic, and $\gamma = \frac{R_{Dt}^o}{R_{Dt}^h}$.

Figure 1. Example of a viral shedding profile for influenza

Simulating the collection of specimens. The simulated collection process is represented in Figure 2. Once individuals get sick from influenza, they seek health care with probability $p_{sh}$. Factor levels $p_{sh}$ are 0.5 and 0.25, and were based on estimates from Internet surveys conducted during the 2009 pandemic.\(^3\) The additional parameters in Figure 2 are justified as follows:

For probability of severity ($p_s$), the following levels were tested: 0.05, 0.15, 0.25. These levels are slightly higher compared to the hospitalization estimates in Shrestha et al.\(^4\) to account for severe cases that were not hospitalized and to better represent scenarios of higher testing demand. The probability of being in a facility ($p_{tf}$) was investigated through sensitivity analysis (level were 0.1, 0.5, 0.9).

The probability that a patient has the ability to pay for an onsite lab test is $p_{wp}$. The levels 0.5, 0.7, 0.9, were used, based on the chances that a U.S. patient has private insurance or Medicaid.\(^5\) Rapid influenza diagnostic tests were not included as part of the simulation as they were not accurate enough to influence physicians’ decisions to submit samples to the VSL.

Simulating the testing of specimens. The aim here was to replicate the operation of one of the real VSL. The extreme theoretical maximum of the VSL in Tampa is around 1000 specimens per day, under pandemic conditions (personal communication, Dr. Lillian Stark, retired virologist from...
the Florida Bureau of Laboratories). Using this upper bound, \( L=300 \) and \( L=600 \) were chosen as more plausible lab capacity levels to be explored in the simulation. The samples sent to the lab are processed on a first-in–first-out policy. If the number of samples received is greater than the lab capacity, the backlog of samples is processed the next day. If a sample waits for 3 days without being processed, it is discarded as unusable. The assumption was that all samples tested are correctly classified as the polymerase chain reaction (PCR) test used has a very high sensitivity and specificity. This testing results in a daily count of confirmed pandemic cases.

**Figure 2.** Process of the collection and submission of influenza specimens to the state viral surveillance labs

**EVALUATION OF THE SURVEILLANCE SYSTEM PERFORMANCE**

The performance of the system was measured through the disease predictive error (DPE), which can be defined as follows:

Let \( u_{kj} \) be the estimator of the reproduction number fitted for the series of pandemic cases, in each factor level combination \( k \), and simulation replicate \( j \).
Let $c_{kj}$ be the estimator of the reproduction number fitted for the series of lab confirmed pandemic cases. Values for $u_{kj}$ and $c_{kj}$ can be obtained respectively with the Lotka-Euler equations:\(^6\)

\[
1 = u_{kj} \sum_{t=0}^{\infty} w(t)e^{-r_{kj}t}
\]

\[
1 = c_{kj} \sum_{t=0}^{\infty} w(t)e^{-r_{kj}t}
\]

Where $r_{kj}$ is the exponential growth rate of the pandemic case series for each $j$ in the combination $k$. A final value of $u_k$ was obtained by averaging the reproduction numbers $u_{kj}$ of all the simulation replicates in the combination. A final value for $c_k$ was obtained similarly. The disease predictive error (DPE) is then calculated as $DPE_k = |u_k - c_k|$. Note that lower DPEs indicate more accurate estimations of the real pandemic trend. Several scenarios were replicated and the DPE was observed in each replicate. Analysis of variance and multiple comparison tests were performed after running the experiment.

**RESULTS**

A total of 108 scenarios resulted from all the possible factor-level combinations (i.e., 2 levels for $p_{sh}$, 3 levels for $p_s$, 3 for $p_{tf}$, 3 for $p_{wp}$ and 2 for L). Each scenario was replicated 20 times. To analyze the effect of factors in the differences between the estimations, a full factorial design of experiments was performed. The test shows that all five factors were significant at 5% significance (i.e., $\alpha = 0.05$). Most of the two-way factor interactions were also significant, with the exception of the interaction between $p_{sh}$ and $p_{wp}$.

From the multiple comparisons tests, we observed that increasing VSL capacity increases the DPE accuracy. This seems reasonable as an increased capacity allows the daily testing of otherwise expiring samples, and refines the estimate of the number of confirmed cases per day. In addition, it was observed that the factor combinations yielding lower numbers of VSL submissions tend to produce more accurate values for the $DPE_k$. For example, as the seeking healthcare behavior ($p_{sh}$) decreases, fewer individuals are eligible for testing ($p_{tf}$), which reduces the number of samples discarded by VSL.

**DISCUSSION**

A screening experiment was performed to explore the effect of different factors in the disease predictive error of a trend of confirmed cases, using an agent-based simulation of disease spread in an urban population. Although the experiment is a very simple abstraction of the reality, it unravels some of the patterns that seem to be true in a real situation of specimen sampling and testing.
To our knowledge, existing VSL receive and test specimens at their order of arrival (i.e., first-in first-out). With this practice, VSL can increase the DPE accuracy if the VSL lab capacity is increased. As it is expensive to increase lab capacity, VSL managers might consider other testing strategies, such as testing as many specimens as the existing capacity permits, and selecting those specimens at random out of the pool of arriving specimens. Another strategy is to forecast the testing capacity by using existing trends such as Google Flu and Flu Near You. Such strategies are still under evaluation and our plan is to provide results on their performance in the near future.

From these findings, what is perhaps more surprising is that the levels of factors that contribute to the reduction of the specimen testing load are contributing to the DPE accuracy. Lower factor levels result in fewer samples submitted to the VSL, which reduces the number of samples discarded. These results might suggest that screening policies for restricting the number of specimens to test seem to also increase the DPE accuracy. Several states implemented these strategies during the 2009 pandemic. For example, in Michigan, specimen testing was restricted by recommending only the submission of high-risk clinical cases (e.g., hospitalized pregnant women and the elderly) to the state labs. Policies like this one might be tested for their impact in the DPE using modeling approaches like the one proposed in this study. If the policies prove to be effective in increasing DPE accuracy, such screening practices might be recommended for routine surveillance.

**SUMMARY BOX**

*What is already known about this topic?* There has been considerable research on estimating confirmed pandemic influenza cases from real outbreak information. However, it is currently unknown whether the influenza surveillance system is capable of producing timely and accurate data for case estimation as the pandemic outbreak progresses. Such information can reduce the uncertainty in the operational decisions to control the outbreak.

*What is added by this report?* This report provides a preliminary evaluation of the surveillance system’s ability to produce timely and accurate case-confirmed data from a pandemic influenza outbreak. This preliminary evaluation showed that each factor tested in the model has a significant effect in the timeliness and accuracy of case-confirmed data. In addition, by the initial observation of the factors, we were able to propose the exploration of policies for more efficient and affordable data collection.

*What are the implications for public health practice, policy, and research?* These results validate current practices for specimen screening and increased testing capacity. However, it is important to consider more cost-effective strategies that could reduce the number of arbitrarily discarded samples and also improve trend estimation. These strategies include: (1) using forecasts to determine how many samples to test using existing online surveillance systems, (2) randomly choosing as many specimens as the capacity permits, and (3) implementing routine specimen screening. Further research is needed to evaluate the previously proposed screening strategies. These methods can be extrapolated to evaluate the surveillance infrastructure under other respiratory viruses with sustained human-to-human transmission such as the respiratory syncytial virus (RSV) and the enterovirus D68.
REFERENCES


