Recommendations for Infectious Disease Modeling

Summary of Scientific Findings - H1N1 pandemic

May 4, 2010
RECOMMENDATIONS

There is general agreement that the 2010 H1N1 pandemic was a test of U.S. systems for protecting the public from a serious influenza outbreak. We all learned a great deal about how existing systems do and do not work. MIDAS investigators are particularly thankful to many groups and agencies that provided data and information throughout the outbreak. We recognize that health agencies were overstretched and greatly appreciate their time and willingness to share. There was also significant sharing of information among the worldwide community of modelers about estimating parameters, now-casting, prediction, effects of behaviors and interventions, and implications of policy decisions.

There remain systemic problems to be identified and addressed. Data acquisition, data sharing, the role of modeling, tension among various goals (e.g., transparency and efficiency), and communication of information are significant challenges for the modeling community. Below are MIDAS’s recommendations to improve the usefulness and timeliness of modeling to support decision making:

Initiate broad discussion on the purpose and organization of infectious disease modeling in the United States.

Improve transparency of decision-making process. It was rarely clear to MIDAS modelers (1) who wanted modeling results, (2) how results were reported, (3) to whom results were reported, or (4) the impact of modeling on policy decisions. It is not clear whether modeling results should be or are reported to CDC, NIH, DHHS, or other levels of decision-making.

Improve communications among modelers and DHHS. It is important to build relationships and develop protocols in advance of an emergency. Modelers need to understand the context in which questions are asked as well as how various policy decisions were prioritized.
- Establish an exchange and/or training program to cross train modelers and DHHS staff
- Involve modelers in discussions on developing modeling questions and scenarios
- Involve modelers in discussions of interpretation and implications of modeling research

Improve data and knowledge sharing among DHHS agencies. There may need to be special rules for expedited sharing in a disaster. Modelers are asked “Where are we now and what do we expect to happen?” Now-casting and anticipation of future dynamics in the absence of good current data are too speculative.
- Develop systems to collect data necessary for planning (e.g., serological surveys, number of people infected or hospitalized)
- Develop systems for analyzing, formatting, and sharing data for a variety of purposes, including modeling
- Develop systems for “reality tests” of model results

Improve the communication of modeling results to non-expert audiences
- Develop, test, and implement better visualization tools
- Improve the presentation of model results to a variety of audiences
**SCIENTIFIC FINDINGS**

**NOTE:** MIDAS is made up of independent, but collaborative, research groups. While there is broad consensus on many points, not all research groups agree on all the findings reported here.

### H1N1 DYNAMICS AND PARAMETERS

<table>
<thead>
<tr>
<th>Description</th>
<th>Organization</th>
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<td>Generation time and incubation period for H1N1 were comparable with seasonal flu.</td>
<td>Fred Hutchison Cancer Research Institute / University of Washington</td>
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<td>As of November, 2009, the US epidemic was growing slowly with R estimated to be ~1.2. The general picture was of low ILI attack rate, low health impact (small percentage of population seeking care), with most transmission in children.</td>
<td>Yale University/ University of Texas</td>
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<td>Determined the reproduction number of H1N1 by analyzing the dynamics of the complete case series in Mexico City. The initial reproduction number (95% CI) was 1.51 (1.32–1.71) based on suspected cases and 1.43 (1.29–1.57) based on confirmed cases before 20 April. The longer time series (through 25 April) yielded a higher estimate of 2.04 (1.84–2.25), which reduced to 1.44 (1.38–1.51) after correction for ascertainment bias. [22]</td>
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Using data from a summer youth camp outbreak, estimated an attack rate of 51% among 96 youth camp participants. A cabin secondary attack rate (SAR) of 41.6% (21.0%-65.7%) and a camp local reproductive number of 2.7 (1.7-4.1) were observed among ≤ 17 year-olds (children). Among the 136 contacts in the 41 households with an index case who attended the camp, the SAR was 10.9% (5.3%-21.0%) and 3.7% (1.6%-8.3%) for children and adults (≥ 18 years). The strong age effect combined with the low number of susceptible children per household (1.2) plausibly explains the lower than expected household SAR, illustrating the importance of other venues where children congregate for sustaining community transmission. [submitted for publication]

Using travel data, estimated that case numbers in Mexico were 2 or more orders of magnitude too low, suggesting that severity there was severely overestimated. [20]

Assisted CDC in developing multiplier models to estimate symptomatic cases and deaths from hospitalizations. [24]

Determined that a key parameter for modeling influenza is the symptomatic rate (the percentage of people who are infected and show symptoms), which is difficult to obtain from current available data, but can greatly impact overall results. [not published]

School-age children typically experience the highest attack rates in primarily naive populations, with the burden shifting to adults during the subsequent season. The group demonstrated that new pandemic strains of influenza are expected to shift the epidemiological landscape in exactly this way. The analysis provides a simple demographic explanation for the age bias observed for H1N1/09 attack rates, and a prediction that this bias will shift in coming months. [in press]

Based on an outbreak in a New York City public school, MIDAS estimated key natural history parameters of the H1N1 virus were estimated including the incubation period, the generation time (also called the serial interval), and the duration of illness. H1N1 was found to have a very similar natural history to previously circulating influenzas. We also characterized the transmissibility of H1N1 by estimating the within school reproductive number, household secondary attack rates, and household transmission probabilities. [18]
Working with North and South America data and the Pan American Health Organization, MIDAS characterized the dynamics of H1N1 during the late spring and early summer in North and South America, estimating the reproductive number of the virus in 19 countries using PAHO surveillance data. A significant association was found between the estimated reproductive numbers and latitude, with more southern locations having higher estimates of the reproductive number, suggesting a strong seasonal component to H1N1 transmission. [in preparation]

Estimated that the case-fatality ratio was between approximately 1/2000 and 1/14,000 symptomatic cases, and provided corresponding estimates of the case-hospitalization and case-ICU ratios. [23]

Using the number of deaths up to a given point in time to estimate the Case Fatality Ratio during an emerging epidemic, one can underestimate by a factor of up to 5 (using parameters similar to 1918). Estimating epidemic’s death toll, incidence, and case fatality ratios before serological data is available is a tricky issue.

MIDAS investigated variability in simulated outcomes due which are due to uncertainty in the social network structure, rather than the disease characteristics or initial conditions. Substantial variability between cities (Miami and Seattle) can be attributed to differences in age and household size distributions. A similar county level analysis for Washington state showed that variability can be attributed to differences in the fraction of school age children, household sizes, and urban/rural contact patterns. Variability across different instances of networks generated by stochastic network models was negligible compared to the variability across different instances of an epidemic on any single network.

MIDAS evaluated possibilities of a “third wave” of H1N1 pandemic. Potential mechanisms evaluated include: (1) wintertime increase of seasonal forcing of transmission with increasing Ro; (2) changes in social contact patterns; (3) progressive viral adaptation with increased human to human transmissibility, and (4) emergence of new immune escape variant. The results showed that increased transmission during a mild epidemic increases attack rate and may lengthen tail; loss of immunity combined with an increase in transmissibility can produce additional peak; vaccination reduces peak and overall attack rate in third wave even with substantial increase in transmissibility and loss of immunity. [not published]

In the period when severity was unclear and unusual measures were under consideration to reduce morbidity and mortality, we defined conditions under which passive immunotherapy could be a successful population-wide strategy. [29]
ANTIVIRAL USE AND DISTRIBUTION

Just prior to the pandemic, MIDAS [28] outlined a strategy to minimize the risk of antiviral resistance spreading using sequential or simultaneous multiple drug treatment at the population level and collaborated with Australian colleagues [21] to translate this into policy recommendations.

Later in the epidemic, MIDAS recommended that predispensing of antivirals to individuals at high risk of complications would under very broad assumptions likely reduce total mortality in the pandemic. [11]

Although a simple pro rata distribution schedule is competitive with optimized strategies across a wide range of uptake and wastage, other equally simple policies performed poorly. More aggressive use of the Strategic National Stockpile could have appreciably slowed the transmission of H1N1 during summer and fall 2009, and thus may be an effective mitigation strategy during the early stages of future flu pandemics.

MIDAS developed simple criteria which ensure that pre-dispensing to certain groups is beneficial for reducing the number of severe outcomes in the whole populations under any scenario on supply and demand of antivirals during an epidemic.

VACCINE USE AND DISTRIBUTION

There is general agreement that pandemic H1N1 vaccine arrived too late to mitigate the epidemic in United States. Had vaccine arrived in September 2009, as originally planned, MIDAS found that over 2,000 deaths and 60,000 hospitalizations could have been avoided. Mass vaccination, along with immunity from the first two waves, may have prevented a third wave of pandemic influenza in the winter and spring of 2010. [submitted for publication]

Under a wide variety of scenarios, an effective vaccination program must start 4-8 weeks prior to the peak of the pandemic, and is greatly influenced by the rate at which vaccine can be introduced into the population. [not published]

When vaccine is distributed during later stages of an epidemic (as it was in case of the 2009 H1N1 pandemic) after sizeable depletion of susceptibles among children has already occurred, vaccination to prevent severe outcomes, particularly among individuals with underlying health conditions, becomes key. We recommended the inclusion of high-risk adults among top priority groups for vaccines. [8]
Optimal vaccine allocation is achieved by prioritizing schoolchildren and adults aged 30 to 39 years. Schoolchildren are most responsible for transmission, and their parents serve as bridges to the rest of the population. Results indicate that consideration of age-specific transmission dynamics is paramount to the optimal allocation of influenza vaccines. [MIDAS not cited]

### Schools and School Closure

The beginning of elevated ILI in the fall of 2009 occurred an average of 14 days after schools opened in a state. The timing of school opening and elevated ILI was highly correlated. This result provides evidence that transmission in schools catalyzes transmission in the entire community. [submitted for publication]

MIDAS investigated the direct economic and health care impacts for school closure durations of 2, 4, 6, and 12 weeks under a range of assumptions. Closing all schools in the U.S. for four weeks could cost between $10 and $47 billion dollars (0.1-0.3% of GDP) and lead to a reduction of 6% to 19% in key health care personnel. [17]

School closure in Hong Kong had a large effect in reducing H1N1 transmission. [4]

### INTERVENTION TARGETING

Maximal reductions in transmission can be achieved by targeting interventions during an epidemic to groups with the highest incidence rate or highest product of incidence rate and force of infection, depending on the type of intervention. [26] A related, analytically optimal approach for vaccine allocation was developed if the vaccine is administered before the epidemic and if the transmission matrix is known. [9]

A vaccination strategy targeting groups whose demographics are correlated with frequency of infection in simulated epidemics can decrease the epidemic peak by 70%, and delay it by 46 days compared to the CDC strategy of targeting age groups, which decrease the epidemic peak by 52%, and delay the peak by 25 days.
**SEASONALITY**

Absolute humidity, previously implicated by laboratory studies as a cause of flu seasonality, could explain the epidemiologic patterns of seasonality in flu for the last several decades in the United States. [25] Using this work and some real-time estimates of transmission in the United States following the October pandemic peak, MIDAS estimated, in response to a BARDA query, that the winter uptick in transmissibility would be unlikely to result in a “second wave” of transmission.

**POLICY ANALYSIS**

In the first weeks of the pandemic, MIDAS defined the likely mismatch in timing between clear evidence of severity/transmissibility and the need to make decisions concerning pandemic response. [8]

MIDAS described a system of surveillance that could implement the WHO summer recommendations to cease counting cases, suggesting a combination of syndromic surveillance and targeted, random viral testing to define the incidence of symptomatic, medically attended infection. [19]

Yearly mass influenza vaccination of school children needs to begin before school opens. [this work was submitted for publication]

After examining a variety of data sources, MIDAS has advocated wider antiviral prescription guidelines for symptomatic individuals in the US.
**ROLES OF MIDAS INVESTIGATORS**

The Harvard School of Public Health Center for Communicable Disease Dynamics took an active part in analysis and response to the 2009 H1N1 influenza pandemic. The PI, Marc Lipsitch, served on the President’s Council of Advisors on Science and Technology (PCAST) Working Group on 2009 H1N1 Influenza and on CDC’s Team B. Members of the CCDD both at Harvard and in Hong Kong provided advice to local, state and national government agencies throughout the pandemic.

The University of Pittsburgh evaluated scenarios as requested by the President’s Council of Advisors on Science & Technology (PCAST) to assist in forecasting health care demand, and in preparation of guidance documents for local and regional planners.

Members of the University of Pittsburgh team were embedded at BARDA to facilitate communication and refinement of modeling activities. A member of the VBI team was embedded at BARDA to facilitate communication of modeling activities and to demonstrate use of tools.

Members of the Fred Hutchison Cancer Research Institute / University of Washington team led WHO working groups on surveillance and vaccination.

The University of Pittsburgh advised the Department of Homeland Security (DHS), providing parameter estimates for National Infrastructure Simulation and Analysis Center (NISAC) modeling, and performing parallel U.S. model simulation runs to compare with NISAC model runs.

VBI advised the Defense Threat Reduction Agency (DTRA) and Northern Command (NorthCom), providing modeling advice and rapid turn-around development for daily briefings at DHHS based on simulations of New York City, Dallas, and Los Angeles.
Collaborators:
Centers for Disease Control and Prevention
Los Angeles County Health Department
King County WA Health Department
Allegheny County Health Department
New York City Department of Public Health
World Health Organization
Pan American Health Organization
Mexico
Canada
Hong Kong Health Department
City of Milwaukee Health Department
United Kingdom Health Protection Agency

Results based on models of
United States
Washington, DC
Los Angeles County, CA
King County Summer Camp, WA
Seattle, WA
Milwaukee, WI
Allegheny County, PA
Dallas, TX
Washington State, county by county
Miami, FL
New York City
Hong Kong


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