



Massachusetts Institute of Technology
Engineering Systems Division

ESD Working Paper Series

Engineering Effective Response to Outbreaks of Influenza

Stan Finkelstein

Senior Research Scientist, Engineering Systems Division, Massachusetts Institute of Technology and Harvard-MIT Division of Health Sciences & Technology
Associate Professor of Medicine, Harvard Medical School
Cambridge, MA USA
Email: snf@mit.edu

Richard C. Larson

Mitsui Professor of Engineering Systems
Engineering Systems Division
Massachusetts Institute of Technology
Cambridge, MA, USA
Email: rclarson@mit.edu

Karima Nigmatulina

Acting Director at the Institute of Master Planning for the City of Moscow
Russian Federation
Email: knigmatulina@genplanmos.ru

Anna Teytelman

Senior Research Staff
Google Inc.
New York, NY USA
Email: teytanna@gmail.com

Engineering Effective Response to Outbreaks of Influenza

Abstract

Objective. Allocation of vaccines and deployment of non-pharmaceutical interventions (NPIs) are critical to controlling influenza. We examine how these policies can minimize the societal impact.

Methods. An engineering systems framing and modeling approach incorporates theories and data on the spread of influenza. Models employed data from the CDC and state governments on cases and vaccine administered during the 2009 H1N1 outbreak, and published literature on how to reduce human-to-human contacts.

Results. During the outbreak, barely half of all states received proportional allotments of vaccine in time to protect any citizens, while fewer sought vaccine after the peak. While individuals prone to contract and spread infection drive the progression, diligent hygiene practices and social distancing measures can drive down the number of cases.

Conclusions. NPIs are highly effective in reducing the spread of influenza before, but also after vaccine is administered. Policies to allocate vaccine in direct proportion to population should be replaced and larger stocks sent to regions where greater numbers of persons stand to be protected.

Introduction

Seasonal outbreaks of influenza are costly in human and economic terms. In the U.S. tens of thousands die each year, and orders of magnitude more worldwide. Annual economic losses have been estimated to be tens of billions of dollars, accounting for costs of medical care and loss of life.¹ Pandemics, occurring much less frequently, have the potential to be more disastrous than an exchange between warring nations. According to historical accounts, the 1918-19 Spanish Flu pandemic killed more than 40 million people; more than died during the First World War.²

Vaccines traditionally have been considered to be the most effective societal interventions to mitigate the impact of influenza outbreaks. Periods as long as six months may elapse while the vaccine is configured, tested, manufactured and distributed. Changes in human behavior with respect to hygiene and social distancing also constitute first-order control of the spread of infections and have been termed, “Non-Pharmaceutical Interventions” (NPI’s). Considered by many to serve as “placeholders” until vaccine becomes available, it is now clear that continual use of diligent behaviors confers great benefits before, during and after outbreaks of contagious illness. Vaccines and NPIs have been incorporated into mitigation policies advocated by public health officials and are widely publicized.

Engineering effective response to outbreaks of influenza aims to derive the greatest value from vaccines, from NPIs and the interaction between these two types of interventions. Current practices for allocating and distributing vaccine are fundamentally flawed, sometimes resulting in its arrival to regions where the illness outbreak has peaked, and where individuals have little interest in becoming immunized. And NPI’s could have even greater impact when targeted at population groups most at risk to transmit or contract illness.

We report findings from models of transmission of influenza that examine alternative policies for the prevention and control on influenza. We argue that a new approach to the distribution of vaccine, coupled with suitably targeted and appropriately timed advocacy of NPIs can save lives, reduce cases and costs, in the event of a seasonal outbreak or pandemic.

METHODS

Engineering effective response to an outbreak requires design of processes to mitigate the seriousness and consequences of the illness and to mount a total system response to it. Components of this approach include effective design of vaccine allocation and distribution processes and developing solutions to anticipated supply chain disruptions that are highly likely to occur. A broad engineering mindset extends beyond addressing well-defined operational issues, to developing new models of disease control. Understanding disease dynamics is key. Influenza disease dynamics are partly under our individual and collective control and any engineered system in anticipation of flu must take this into account.

We constructed mathematical models that afford the evaluation of the effectiveness of vaccines and also both government-imposed and individually elective behavioral measures, including social distancing and personal hygiene practices. Following is a review of the key concepts incorporated into the models and the sources of data used in their execution.

CONCEPTS UNDERLYING THE MODELS

REFLECTING ON R_0 , THE REPRODUCTIVE RATIO. A critical parameter used in almost everyone's modeling of influenza transmission is R_0 , the *basic reproductive ratio* or *basic reproductive number*, usually defined to be the average number of new infections generated by a "typical" infected person in a population of 100% susceptible individuals. Note that R_0 is an *average*, implying that it has a probability distribution whose mean is R_0 . Early in the outbreak, R_0 is the average growth factor, "generation to generation" of newly infected individuals. An R_0 of 2, for instance, would indicate that early in the outbreak an average infected person transmits the disease to an average of two others. Any R_0 less than 1.0 virtually guarantees that the illness will die out. A near-term exponential increase in the number of people who will become infected with the flu is usually associated with an R_0 value greater than 1.0. But even the concept of R_0 is problematic, as we discuss below.

A significant issue with the flu is that an infected and infectious person can be asymptomatic for a day or more, unknowingly spreading the flu to others, and only later come down with flu symptoms – at which point he or she will most likely self-isolate and most often eventually recover. This fact makes R_0 larger than it would have been, had there been no asymptomatic infectious period prior to arrival of flu symptoms.

How is R_0 determined? The World Health Organization (WHO) and U.S. Centers for Disease Control and Prevention (CDC) often 'announce' the R_0 value for a new flu virus. For instance, the numerical values estimated for R_0 for the 2009 H1N1 flu tended to be between 1.4 and above 2.0.³ These announcements and associated research papers seem to assume a world in which R_0 is beyond human control, as if R_0 were "nature's constant" associated with a given virus. But Larson demonstrated that R_0 can be represented in terms of human behavior *and* the innate characteristics of the virus. The relationship involves an infected person's frequency of human-to-human contact (λ) and his/her conditional probability of transmitting illness (p), given close contact, as follows:

$$R_0 = \lambda p. \tag{1}$$

This simple equation shows that R_0 is a function of both the inherent properties of the given virus – as represented in part by p – *and* the population's behavioral responses to it – as represented by λ and also by p .

How do we reduce λ and p ? One reduces λ simply by having fewer face-to-face contacts each day. What about p ? Vaccines are probably the best-known way of reducing p . But p is a function of three factors: (1) the innate infectivity of the virus; (2) the hygienic practices of the infected and infectious individual having the close contact; and (3) the vaccine status and hygienic practices of the non-infected but possibly susceptible individual on the other side of the close contact. While (1) is uncontrollable, (2) and (3) represent opportunities to reduce the likelihood of passing the infection along to the individual who is susceptible without vaccine. NPI examples including personal hygiene practices such as frequent aggressive hot-water hand washing and not touching one's face with one's hands. Social distancing also plays a critical role, as in avoiding handshakes, perhaps bowing instead. In our models, R_0 is a key measure incorporating the range of determinants of the spread and control of an infectious outbreak.

STOCHASTICITY. While R_0 provides an easy and computationally intuitive basis for describing disease dynamics, it has a number of limitations, and these tend to be distributional. First, as mentioned above, R_0 is the mean of a probability mass function. Consider an R_0 value of 2.0. At one extreme, all the probability may be located at 2, and with deterministic regularity each newly infected person early in the pandemic would infect exactly 2 others. But that is idealistically simplistic, and no human population would behave in such a robotic manner. More likely, the probability mass function might resemble a geometric function, starting at 0 and having mean 2. Such a function anticipates a great deal of variability on the number of new infections generated by any infectious individual. And one can think of limiting cases at the other extreme with most probability located at zero and with a small amount at a large number such as 40, with mean still equal to 2. This type of situation involves so-called 'super-spreaders' who if active early in the pandemic can catapult it to major status but who if they do not appear early will result in a flu that dies out rapidly, even with an R_0 value of 2. So, we must remember that R_0 is the mean of a distribution and its variance and in fact entire functional form will have a huge role to play the evolution of the disease.

HETEROGENEITY. In addition to stochasticity, we have another distributional issue with R_0 – heterogeneity of the population. Members of a population are heterogeneous with respect to their personal characteristics and their behaviors. In a sense, each person in the population has his or her "own" value of R_0 . And this is to a large extent under the control of the individual. A possibly infectious grocery store checkout clerk who interacts with perhaps hundreds of persons each day can, by staying home for a day, greatly reduce her personal R_0 . And during a workday, she can reduce her R_0 by not touching people directly and by washing hands with hot soapy water frequently.

As an outbreak of influenza evolves, decision makers receive aggregate statistics in the form of the number of people reporting to physicians with flu-like symptoms, number of related hospital admissions, number of flu-related deaths, and number of vaccinations administered. Yet, aggregate statistics hide the fact that early

transmission and propagation of the disease are driven largely by particular segments of the population: (1) those who are highly active in daily face-to-face encounters; (2) those who are overly prone to become infected given exposure; and (3) those who shed virus and spread the disease more than average. Any person can be characterized along a spectrum of these three attributes: social activity, proneness to infection, and proneness to shed virus and spread infection. Those who are at the 'right-hand-tails' of one or more of these distributional attributes play a significant role in the early spread of the disease. Such individuals, due to early infection and later immunity, drop out of the susceptible population near the middle and almost certainly by the end of the outbreak.

The best available data on human contacts is from two published sources. Fu reports a study of 3000 respondents from nine countries and 46 different settings who were asked to estimate daily personal contacts, including face-to-face, telephone, mail and Internet. In a separate study, for Taiwan only, Fu found that 83% of reported contacts were face-to-face⁴⁵. In a separate report, the Mossong group conducted a thorough study of contacts by participants in eight European countries. Participants were asked to record their daily contacts, defined as either "skin-to-skin" or a two-way conversation with three or more words in the physical presence of another person. The information from participants' diaries was weighed to match the demographics of participating countries. The group published distributions of daily contacts by individuals from each country.⁶ We incorporated data from four of those countries, Belgium, Great Britain, Germany and Poland into our models and subsequent analysis.

Population heterogeneity due to widely differing frequencies of social contacts and also due to infection proneness and to virus shedding behavior plays a key role in the speed of infection spread aside and brings into question the estimation and even definition of R_0 . It is reasonable to assume that people who are most susceptible to infection are also those that are most likely to spread it to others; the most socially active people combine these two attributes. To understand the dynamics of flu spread, or the spread of any human-to-human infectious disease, one must account for such population heterogeneities. With regard to R_0 , people who have one or more of these attributes largely drive the early exponential growth of the disease: socially active, infection-prone and efficient virus shedders. This suggests that our definition of R_0 , if it is to represent the generation-to-generation early exponential growth of the disease, needs to be more nuanced than simply: "...average number of new infections generated by a 'typical' infected person in a population of 100% susceptible individuals." "Typical" is too vague. One suggested change is to replace "typical infected person" with "typical face-to-face interaction with an infected person." Such a change would automatically account for those early in the disease growth with greater-than-average social activity – focusing on interactions and not individuals.

Most published models of population heterogeneity utilize ‘compartmentalized models,’ in effect discretizing the population and placing each person into one of a finite number of homogeneous segments. Larson and Teytelman⁷ generalize that approach to eliminate the need for a finite number of discrete classes of statistically identical individuals, and instead, introduce a continuous distribution for all the key parameters in question, in essence employing an infinite number of classes. Their generalized model deals with all three attributes introduced above: social activity, proneness to infection, and proneness to spread infection. The model relies on just a few equations that define the state of infection at a given time.

Model structure

The most common models for influenza spread follow some variant of the S-I-R compartmental approach, where each person is susceptible, infected, recovered (or deceased). These models are most-often used in a homogeneous setting, where all people in a compartment behave identically, and mix randomly. One may call the approach “models of statistical clones.” As discussed above, this approach is incomplete because it ignores heterogeneity, of which a well-known example is the notion of “super-spreaders”. More typical are populations in which some members more actively spread or contract illness than others. Our approach has been to use discrete-time models and to account for heterogeneity via proportional mixing, where an individual is likely to become infected in proportion to his or her contact rate. We introduce a continuous distribution for three parameters of interest – social activity, proneness to infection and proneness to spread infection. The initial focus is on contact rates, the available measure of social activity. The model relies on difference equations that define the state of infection at a given time and allow the calculation of $R(t)$, the analog of R_0 at any point in time, as the outbreak evolves. The unit of time is a generation of influenza, defined here as the two-to-three day period during which a person becomes infected and soon infectious and interacts in society. $R(t)$ is defined as the mean number of new infections caused by a ‘typical’ infected person during generation t of disease progression. Since more and more people become immune to infection as the disease progresses, due to vaccination or to recovery and hence immunity to further infection, we always have or any flu generation $t > 1$, $R(t + 1) < R(t) < R_0$. That is, the exponential rate of growth slows, grows less than exponentially, eventually stops growing (when $R(t) = 1$), and then declines. The full formulation of the model has been published elsewhere.⁸

HUMAN CONTACT AND BEHAVIOR. When studying and modeling sexually transmitted diseases, especially HIV/AIDS, behavioral changes are often cited as the main factors determining transmission dynamics, but when it comes to modeling flu, behavior is almost always ignored. This is puzzling, and in our opinion quite an incorrect approach. Few would dispute the observation that people alter their behavior during an outbreak by adopting more diligent hygiene, and by decreasing their frequency and intensity or closeness of human contacts. Recent history has provided us with multiple examples of people responding to news of a disease by altering their daily behavior.

Consider the example of the social behavior changes that occurred during SARS in Hong Kong, 2003. One survey indicates that during the SARS outbreak in Hong Kong 87% of the population covered their mouths while sneezing or coughing, 76% of individuals wore masks, 65% washed their hands after contact with possibly contaminated objects. Residents who thought that they might have been exposed to SARS voluntarily self-isolated for up to ten days. Economic factor studies in SARS-affected cities of Hong Kong, Beijing, Singapore and Toronto indicate that there was a sharp drop in interactive social activities as restaurants and entertainment centers suffered plummeting numbers of clientele. Specifically in Hong Kong, tourism was crippled in March 2003 when the WHO issued a rare warning for travelers to avoid Hong Kong and China's Guangdong Province. As a result of weakening demand, airlines slashed more than a third of flights, and hotels in Hong Kong reportedly were up to 90% empty. But SARS was stopped, and yet no pharmaceutical cure was found.⁹

To the best of our knowledge, the eradication of SARS was due to collective behavioral changes of the overall population and of medical caregivers, in effect causing R_0 to drop significantly below 1.0. This represents an existence proof that R_0 can be largely determined by individual and collective behavioral change. *This is a profound result.* It suggests that R_0 is not defined in the abstract as a constant of any given infectious disease. To be concrete, it makes no sense for the WHO or the CDC to state publicly that a new influenza virus is circulating the Earth with an R_0 value of, say, 1.432. Rather, the local population and their individual and collective behaviors contextually determine R_0 . In the future, it is entirely plausible that when a novel virus surfaces there will be communities for which R_0 is less than 1.0 and other communities, such as those living in close and closed quarters, where R_0 could exceed 2 or 3 or more.

DATA

Disease dynamics and vaccine distribution. We applied our modeling approach using data from the CDC and state health departments from the 2008-09 outbreak of H1N1 influenza. We estimated the epidemic curves for the US as a whole and for 48 states with influenza-like-illness (ILI) data, obtained from state health departments. The CDC considers ILI data to be an effective means of following the dynamics of progression of the outbreak. Sentinel sites report the proportion of outpatient visits, hospitalizations and deaths associated with ILIs to the CDC via ILINet, an online reporting system.¹⁰ The CDC tabulates these data on national and regional levels and publishes results weekly in *FluView*.¹¹ We compared the epidemic curves we derived with two sources of vaccine distribution data. The first is vaccine shipment data, which track, for all fifty states, the number of doses of vaccine shipped to each state over time. The second source provided data on vaccine actually administered, as each healthcare provider was required to report numbers of flu vaccinations administered by state and local health authorities before being given additional vaccine. We obtained this latter information from individual health departments of nine states.

Results

Illness dynamics and vaccine allocations as delivered

As previously reported, during the 2008-09 outbreak of H1N1 influenza, in 24 of 50 states, the outbreak had already begun to decline before individuals were actually protected by vaccination immunization. Further, among 11 states, no more than 2% of the state's residents were vaccinated before the outbreak had peaked.

For each of eleven states, our model was fitted to the reported ILI data to create two separate model-estimated epidemic curves: the first assuming no vaccines delivered and the second incorporating actual vaccine administration data for the state. We also generated a third model-based epidemic curve, one showing the curve if the vaccine had been delivered two weeks earlier than actual. We were then able to infer the proportion of infections that (1) were averted due to the administration of vaccine, even if late; and (2) would have been averted if the vaccine supplies had been received two weeks earlier. Averted infections ranged from as much as nearly 14% of the population in Massachusetts, where the outbreak occurred later, to as little as 0.14% in Mississippi which experienced a much-earlier outbreak.

Discussion

To engineer an effective response to an outbreak of influenza, one would deploy technology (e.g., vaccine) and effect changes in human behavior, in order to reduce the contract rate and the probability of illness transmission. Both NPI's and vaccines are, of course, key components of the public health response.

It is unlikely that society will implement severe measures as they did in 1918-1919 making it "unlawful to cough and sneeze" punishing violators with up to a year in jail. However, even without forceful implementation people are likely to try to decrease their likelihood of becoming ill by improving hygiene related behaviors. We control the contact rate, for example, by switching from daily to weekly grocery shopping, or, better yet, to having groceries delivered to one's door. If you manage a team of employees, rather than having face-to-face meetings during a flu emergency, have conference calls instead, with many workers telecommuting. Many companies have already created comprehensive pandemic flu plans that include telecommuting, reduced face-to-face encounters and even increased desk spacing between workers.

Vaccines and NPI's both contribute to reducing the probability that any given face-to-face contact will result in a new infection. Wash hands with hot water and soap several times daily. Do not shake hands during greetings with colleagues. Cough or sneeze into your elbow, not into the open air or your bare hand. Be careful not to touch surfaces that might have recently been contaminated with flu virus. Encourage your city's large employers to stagger work hours, so that public transportation subways and busses are less crowded during now-stretched-out rush hours. Even run the subways and busses with windows opened.¹²

Targeting High Activity Populations

As we have discussed, the at-risk population is heterogeneous in its social activity and in its susceptibility to contract and transmit illness. Of particular interest is to consider how social behavior influences the propagation of disease. The model results demonstrate convincingly that targeting high activity population components have the greatest role in transmitting illness and can have great impact on how quickly the outbreak can be controlled.

High activity members of a population can contribute to mitigating the effects of an outbreak by accepting vaccine to reduce their own susceptibility and transmissibility, by reducing human contacts, and by adopting NPIs to reduce transmissibility.

Vaccines offer greatest societal benefit when administered early to highly active population members. This observation should be considered when constituting “high risk” groups to be offered early access to immunization. In addition to first responders, health care workers, elderly and chronically ill, a portion of the first available doses of vaccine might be targeted to those individuals having large numbers of daily human contacts.

Diligent personal hygiene among high activity persons benefits not only themselves, but also others with whom they have contact, and can have a disproportionate role in reducing spread. Hence, there should be great value in targeting these same groups with messaging to adopt NPIs.

How to target persons having high frequencies of human contacts? Public health practices commonly address school age children and others spending time in closed and confined quarters. Those who make use of our various transportation networks are also thought of as potentially disproportionate illness transmitters. Consideration has been given to imposing travel restrictions, however, many published articles suggest that it offers low payoff, at best.¹³

Users of all forms of public transportation – subways, trains, buses and planes – can be considered “high activity” and targeted for behavior change, that can include, depending on outbreak severity, encouragement to take vaccine and practice various NPIs. Short of any mandated shutdown of transport networks, voluntary measures, if adopted, could prove to be major contributions to control of an outbreak. Potential benefits from this approach extend to individuals engaging in private modes of transportation, including taxicabs, carpools and even solo commuters, who come in contact with others at gasoline stations and fast food restaurants.

The bottom line is that targeting members of a highly active population group to change behavior is likely to be more successful than a broad public campaign. This has proven true in the marketing of many consumer products and in screening for

treatable illness, and would be very worthwhile in the control of outbreaks of infectious disease.

Vaccine Allocation

In the 2009 H1N1 pandemic, vaccines arrived late. This is not surprising due to the six or more month delay between identifying a novel flu virus, inventing an appropriate new vaccine, and manufacturing it for distribution. The pandemic was already well underway in the U.S. when vaccine distribution commenced in October of 2009. Early deliveries were rationed and delivered to collections of states (“regions”) by the CDC in direct proportion to each region’s census population, regardless of the status of the flu wave in the region. This deployment method is at least partly driven by perceptions of equity and other “political” considerations.

We conjecture that the timeliness of vaccines is closely related to the proportion of the population who will accept vaccines. During the 2009 H1N1 outbreak in Mississippi, for example, less than 40% of its allocated vaccine was used, most likely due to “flu fatigue”. South Carolina managed to immunize only 8% of its population. Had vaccine been available and delivered there before the outbreak peaked, its effectiveness would have been greater with respect to both disease dynamics and participation rate. Similar observations can be made about the experience of many other states, especially in the U.S. southeast, where schools open in August and the flu waves started then.

Our model results suggest that incorporating an adaptive component to the allocation of vaccine during an outbreak will reduce the eventual number of infections. The peak of an infection is expected to occur when “herd immunity” is achieved, after which every contagious person infects, on average, one person or fewer. Early administration of vaccines, with respect to the eventual peak of the outbreak decreases the number of individuals who remain to be infected or protected. Late administration has marginal effect on the dynamics of an initial outbreak, but could still prove to be important, if flu returns in a later wave.

Our model results suggest that the CDC’s population-based flu allocation approach is far from optimal, as it does not attempt to minimize the total number of flu infections that will occur nationally. Rather its objective function is to equalize per capita distribution of the vaccine regardless of its potential flu-averting benefits nationally. A better policy would be to allocate vaccine not in proportion to state populations, but to vulnerable regions that have seen fewer cases, that will have a higher fraction of its population susceptible, and thus where a vaccine can avert the maximum number of future infections. Our flu vaccine deployment method, if it had been used in 2009, would likely have averted about 7,000,000 of the estimated 21,000,000 Americans infected with H1N1 flu.¹⁴

Limitations

The full formulations of the models and interpretation, as well as limitations of the analyses have been published elsewhere.^{15 7813}

CONCLUSION

Outbreaks of influenza can be grave threats to lives and to the security of our homeland. A great benefit of our efforts to engineer effective response to seasonal outbreaks of influenza or pandemic influenza, is that it forced a logical and systematic consideration of all aspects of the problem. The value of immunization is greatly enhanced when it is deployed in relation to the dynamics of the progression of the illness. The benefits from diligent personal hygiene and social distancing, while widely recognized, can be much greater if public education initiatives are targeted toward population members having disproportionate numbers of human contacts. We are hopeful that the approaches we have described and the results obtained offer the prospects of mitigating the future impact of these kinds of adverse events.

ACKNOWLEDGEMENTS.

Work on this paper was supported by the Sloan Foundation of New York under a grant entitled, “*Decision-Oriented Analysis of Pandemic Flu Preparedness & Response*,” and under a cooperative agreement with the U.S. Centers for Disease Control and Prevention (CDC), grant number 1 PO1 TP000307-01, “LAMPS (Linking Assessment and Measurement to Performance in PHEP Systems), awarded to the Harvard School of Public Health Center for Public Health Preparedness (HSPHCPHP) and the Massachusetts Institute of Technology (MIT), Center for Engineering Systems Fundamentals (CESF). The discussion and conclusions in this paper are those of the authors and do not necessarily represent the views of the Sloan Foundation, the CDC, the U.S. Department of Health and Human Services, Harvard or MIT.

REFERENCES.

-
- ¹ McKibbin, W. Global macroeconomic consequences of pandemic influenza. Lowy Institute for International Policy, Sydney.
<http://www.lowyinstitute.org/Publication.asp?pid=345>. Published February 2006. Accessed March 4, 2010.
 - ² Pandemic flu history. Flu.gov website.
<http://www.flu.gov/pandemic/history/index.html>. Accessed March 4, 2010.
 - ³ Prachayangprecha, S, Makkoch, J, Payungporn, S, et al. Serological analysis of human pandemic influenza (H1N1) in Thailand. *J Health Popul Nutr*. 2010;28(6):537-544.
 - ⁴ Fu, Y.-C. Measuring personal networks with daily contacts: A single-item survey question and the contact diary. *Soc Networks*. 2005;27:169-186.
 - ⁵ Fu, Y-C. Contact diaries: Building archives of actual and comprehensive personal networks. *Field Methods*. 2007;19(2):194-217.
 - ⁶ Mossong, J, Hens, N, Jit, M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med*. 2008;5(3):e74.
 - ⁷ Larson, R, Teytelman, A. Modeling the effects of H1N1 influenza vaccine distribution in the United States. *Value Health*. 2012;15:158-166.

-
- ⁸ Larson, R, Teytelman, A. Modeling influenza progression within a continuous-attribute heterogeneous population. *Eur J of Oper Res.* 2012;220(1):238-250.
- ⁹ Lo, JYC, Tsang THF, Leung, Y-H , Yeung, EYH, Wu T, Lim, WWL. Respiratory infections during SARS outbreak, Hong Kong, 2003. *Emerg Infect Dis.* 2005;11(11):1738-1741.
- ¹⁰ Centers for Disease Control and Prevention: Sentinel Home Page. <http://www2a.cdc.gov/ilinet>. Accessed July 29, 2010.
- ¹¹ Centers for Disease Control and Prevention: CDC, Seasonal influenza (flu), Weekly Report: Influenza summary update. <http://www.cdc/flu/weekly/>. Updated May 28, 2010. Accessed July 29, 2010.
- ¹² Finkelstein, S, Prakash, S, Nigmatulina, K, McDevitt, J, Larson, R. A home toolkit for primary prevention of influenza by individuals and families. *Disaster Med Public Health Prep.* 2011;5(4):266-271.
- ¹³ Nigmatulina, K, Larson, R. Living with influenza: Impacts of government imposed and voluntarily selected interventions. *Eur J of Oper Res.* 2009;195:613-627.
- ¹⁴ Larson, R, Teytelman, A. Modeling the effects of H1N1 influenza vaccine distribution in the United States. *Value Health.* 2012;15:158-166.
- ¹⁵ Larson, R. Simple models of influenza progression within a heterogeneous population. *Oper Res*, 2007;55(3):399-412.