MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **8**, Number **1**, January **2011**

doi:10.3934/mbe.2011.8.1i

pp. **i–vi**

PREFACE

A new A/H1N1 influenza virus strain was officially reported/identified in Mexico City on April 13 2009 and over a period of two-weeks the WHO pandemic alert was moved from level 3 to level 5. By May 2, a total of 141 cases had been confirmed in 19 states across the USA. Additional cases were soon confirmed in fifteen countries in Europe, Canada, New Zealand, and Asia. The global reach of this novel strain became evident when a summer influenza incidence high was reached in Japan by May 16, 2009 [2, 4] just about a month after its identification in the New World.

Efforts to identify the origin of the 2009 A/H1N1 novel virus strain engaged several scientists immediately[5, 6]. Preliminary reports identified similarities between the 2009 and the 1918 H1N1 influenza pandemics [1]. Most of the relatedness arguments were based on the reported age-distribution of *severe* cases since a large percentage of them seemed to involve young adults [3, 8, 7, 10]. The 1918 A/H1N1 outbreaks (we were reminded, often even by the press) were followed by a second "wave", the first driven by what appeared to be a *mild strain* in the spring and a more *virulent strain* outbreak in the fall [8, 9].

The importance of implementing policies to mitigate the impact of the 2009 pandemic was pressing. We were aware that the second 1918 A/H1N1 waves were responsible for a large percentage of the influenza-related deaths (over 90% according to some reports). Whether or not the final course of the 2009 pandemic would match or even resemble the patterns of the 1918-1920 ("Spanish influenza"), or the 1957-1959 (Asian influenza), or the 1968-1970 (Hong Kong influenza) pandemic outbreaks was not known but *the potential* raised valid concerns that had to be addressed by policy makers under high levels of uncertainty. The predictions of a severe second wave did not materialize. In fact, the second wave in Canada, while much bigger than the first, was indeed milder [14] and that was a good thing.

By the start of 2010, it had become evident that this *pandemic* belonged to the mild category to the point that its impact began to be compared to past seasonal influenza outbreaks. Clearly, some of the elements of the WHO pandemic definition turned out to be insufficient since for example, they did not incorporate measures of disease severity. In fact, the WHO definition seemed to be primarily based on the ability of the virus to *invade* susceptible populations at a *global scale*. The WHO pandemic definition was put under the microscope. It should clearly be revised.

The limitations of WHOs pandemic definition have now been quantified at a level of resolution that exceeds those used to evaluate past pandemics. The issue of severity has entered into the analysis. Seasonal influenza, for example, is reported to be responsible for about 35,000 deaths during the winter season in the US alone with the majority of the victims being infants and the elderly [11]. Consequently, the risk associated with this pandemic is being measured in relation to the average severity of past "seasonal" influenza outbreaks. The mildness of this pandemic seemed to have already been factored in by theoreticians who were asked to forecast its consequences. *Time* reported just about a year ago that: "Marc Lipsitch, an

epidemiologist at the Harvard School of Public Health, and his colleagues studied the course of the 2009 H1N1 pandemic last spring in two cities New York and Minneapolis and determined that 0.048% of people who developed symptoms of H1N1 died, and 1.44% required hospitalization. Based on that data, published in PLoS Medicine, Lipsitch anticipates far fewer deaths from 2009 H1N1 than was initially believed. By the end of the flu season in the spring of 2010, Lipsitch predicts, anywhere from 6,000 to 45,000 people will have died from H1N1 in the U.S., with the number most likely to end up between 10,000 and 15,000. Those estimates are far below the death toll of the 1957 flu, which killed 69,800 people in the U.S., according to government figures, and smaller also than the early predictions for the 2009 H1N1 flu deaths, which ranged from 30,000 to 90,000."

The official public health responses to what turned out to be a mild pandemic brought into light the limitations and/or deficiencies of local, national, regional, and global response policies. Using a hurricane analogy, it became obvious that, while we should always hope for a "Rita" we must be prepared for a "Katrina".

The current successes in mitigating the impact of seasonal influenza (vaccine, antiviral drugs, and improved health practices and services) brought back additional concerns. For example, the potential indiscriminate global use of antiviral drugs not only provides additional opportunities for selection [13] but in fact, it is quite possible that its overuse or over prescription, in times of uncertainty, may accelerate it. Increases in the levels of drug resistance could make an important line of defense not only less effective but potentially useless. The lack of a global policy responding effectively to global health emergencies is evident particularly when these challenges are seen from a global perspective that considers influenzas responses to evolutionary pressures [15, 16].

The collection of articles in this volume explores some of the consequences of policies constrained by the limited ability to respond effectively (levels of preparedness) to the A/H1N1 2009 pandemic at a global scale. The volume highlights challenges and opportunities that need to be addressed jointly by the scientific and public health communities. Questions raised include: How useful has our knowledge of past pandemics been in dealing with this global outbreak? What is our current state of preparedness? How do we manage a limited supply of antiviral drugs or vaccines? What is the impact of mass transformation systems (air-traffic and other) on influenza dynamics? What are the lessons learned from observed international mitigating efforts? How should severity be factored in the definition of a pandemic?

Soon after the onset of the 2009 influenza pandemic in Mexico, a group of biostatisticians, mathematicians, and public health officials primarily from Canada, Mexico and the United States gathered in Tempe Arizona at a four-day workshop in June 25-28, 2009. These researchers looked closely at incoming pandemic data while introducing models to assess its impact. The driving goal of this effort has been to identify ways of assessing the magnitude and mitigating the impact of this pandemic. At the 2009 SIAM annual meeting (July 7-9, 2009), a special session was held by members of this group. A meeting involving a large number of international influenza researchers, was subsequently held in Vancouver, Canada (September 14-16, 2009).

The contributions of some of the scientists that participated in these gatherings are collected in this volume. They form the basis for the discussions that will take place at the Centro Internacional de Ciencias, Cuernavaca, Mexico, in January 9-16, 2011. Scientists from Canada, Mexico and the USA will meet to evaluate

what has been learned over the past 18 months. Researcher will use this meeting to re-energize transnational collaborations on the study of the transmission and evolutionary dynamics of influenza. It is the expectation that these efforts will be carried out in collaboration with public health officials of these three nations. The volume provides a self-contained collection of articles that serves at least two purposes: (i) highlight the research driven by this recent influenza pandemic and (ii) provide a centralized collection of contributions aimed at a wide community of young researchers interested in the study of influenza epidemics.

In the first paper, Arino et al. provide an overview of mathematical modeling of the spread of infectious diseases with a focus on applications to pandemic influenza. The authors discuss lessons learned and key insights from the application of mathematical modeling to epidemic spread and "the complications arising from attempts to apply it for disease outbreak management in a real public health context." Herrera-Valdez et al. identify potential mechanisms responsible for the three "waves" observed in the A/H1N1 Mexico data. These researchers explore the role of mass-regional transportation systems and government mandated or naturally initiated social distancing measures on the generation of Mexico´s incidence influenza patterns throughout 2009. The relative *minimal* impact of a late arriving vaccine is also discussed. Nishiura´s contribution focuses on a pandemic that "offers an opportunity to jointly quantify transmission dynamics and diagnostic accuracy via a joint estimation procedure that exploits parsimonious models to describe the epidemic dynamics and that parameterizes the number of test positives and test negatives as a function of time." The method is first shown to be effective if used against 2007-2008 A (H1N1) Japanese data and then it is put to work on 2009 Tokyo-Narita airport screening data. The value of reporting both test positive and test negative cases consistently is highlighted.

Reichert starts from the premise that current "Specific recommendations for protection [US population] embody a bunker mentality with a time horizon of two weeks, emulating preparation for a natural disaster. The epidemiology of pandemic influenza is scarcely considered." Reichert discusses the feasibility of protecting institutions (within a society or community) against a disease introduction with widespread levels of severe infections, that is, the type of scenario attached to influenza pandemics of high levels of severity. Reichert focuses on scenarios where only the rigorous implementation of sequestration-in-place regimens coupled with decontamination and quarantine procedures for re-entry together with wearing barrier protection in the external world may avert catastrophes. In other words, Reichert addresses social disruption dynamics as a function of pandemic severity.

The unavailability of a vaccine at the start of this pandemic provides ample proof of the world´s inability to produce the substantial number of dosages needed to protect against pandemic influenza from a global perspective. Roy Curtiss III, a world expert in the design, construction and evaluation of genetically modified recombinant attenuated Salmonella vaccines administered intranasally or orally brings to the forefront the challenges and opportunities for modelers raised by the efforts of his group to develop vaccines that prevent infections by Streptococcus pneumoniae, Mycobacterium tuberculosis, human and avian influenza and other diseases. In addition to describing major infectious diseases and the current status for control by vaccination, Roy Curtiss III also discussed the barriers to infection and the attributes of innate and acquired immunity contributing to control. Moreover, the

evolution in types of vaccines is presented in the context of developing technologies and in improving adjuvants to engender enhanced vaccine efficacy. The special concerns and needs in vaccine design and development are also discussed in dealing with epidemics/pandemics with special emphasis on influenza and current global problems in vaccine delivery.

At the population level the question of who should be vaccinated first in the absence of unlimited supplies or delays in delivery needs to be addressed. Should we first vaccinate those with high-risk complications or individuals that must be protected so that we have a functioning society? The world´s limited capacity to produce enough A (H1N1) vaccines made the decisions taken during the past pandemic difficult. Further, delays in vaccine development, production and delivery made it nearly impossible to respond effectively in a timely manner. Furthermore, in a highly heterogeneous world, these decisions had to be made under different constraints. Shim introduces an age/risk- structured model of influenza transmission parameterized with epidemiological data from the 2009 influenza A (H1N1) pandemic. Her model predicts that the impact of vaccination would be diminished substantially if delays prevent timely access to an adequate vaccine supply. "Nonetheless, prioritizing limited H1N1 vaccine to individuals with a high risk of complications, followed by school-age children, and then preschool-age children, would minimize an over- all attack rate as well as hospitalizations and deaths." Bowman et al. use an epidemic model to study the effects of single and two-dose vaccination strategies on disease dynamics. They show, for example, "that, if vaccination starts early enough after the onset of the outbreak, a two-dose strategy can lead to a greater reduction in the total number of infections" as long as the second dose confers a substantially higher protection than the first dose. Knipl et al observe "Finding optimal policies to reduce the morbidity and mortality of the ongoing pandemic is a top public health priority." They proceed to introduce a compartmental model with age structure that keeps track of the vaccination status. These authors examine "the effect of age specific scheduling of vaccination during a pandemic influenza outbreak, when there is a race between the vaccination campaign and the dynamics of the pandemic." They conclude their study through a careful assessment of the issues of timing and age-specific vaccination policies.

The identification of public health policies that minimize the relative cost of interventions resulted in three contributions that apply optimal control theory two three distinct scenarios derived from what was observed during the 2009 A (H1N1) pandemic. Prosper at al. focus on the challenges faced by communities dealing simultaneously seasonal and novel A-H1N1 co-circulating strains outbreaks. Prosper et al.´s study is carried out in an environment where individuals have no access to novel A-H1N1 vaccine supplies, a limited access to a seasonal influenza vaccine supply, and a limited supply of antivirals like Tamiflu. The identification of optimal intervention policies means that controls, giving the existing information, account only the relative (rather then the absolute) costs associated with the implementation of each policy. The impact of an intervention policy based on the relative costs of interventions is analyzed when the choice is either social distancing measures or access to antiviral treatment or a combination of both (the "right" combination). Lee et al. start from the position that the world´s limited capacity to produce an adequate vaccine supply over a short-time horizon (a few months) must be factored in. These authors´ research quantifies the role of restricted vaccine-level supplies in the implementation of effective public health policies when cost is critical. Gonzalez-Parra

et al identify the best ways of reducing morbidity and mortality at the population level at a minimal relative cost. "The problem is solved by using a discrete version of Pontryagin´s maximum principle." Numerical results are used to highlight that the use of dual rather than single intervention strategies has stronger impact if the goal is to reduce the final epidemic size.

Rios-Soto et al. step back and look at the dynamics of influenza reservoirs. These researchers focus on the interactions between transient and resident bird populations (a key genetic human-influenza reservoir) in order to throw some light on the role of the dispersal on avian influenza dynamics. Rios-Soto et al. show that mixing between residents and migratory bird populations and residence times (driven by migratory patterns) play a critical role on the patterns of avian influenza spread. Acuña-Soto et al. provide an epidemiological historical account of the 1918 influenza pandemic in relation to the recent 2009 H1N1 influenza pandemic. Their detailed chronological description of the 2009 H1N1 influenza pandemic in Mexico focuses on the detection of severe respiratory disease among young adults in central Mexico. This description is followed by an account of the efforts carried out by Mexican epidemiologists to identify a novel swine-origin influenza virus as well as the response of Mexican public health authorities. Potential similarities between the 1918-1920 and 2009 H1N1 influenza pandemics in Mexico are also addressed.

Carlos Castillo-Chavez and Gerardo Chowell-Puente
Tempe, Arizona, USA

REFERENCES

[1] J. Cohen, "Swine Flu Pandemic Reincarnates 1918 Virus, 24 March 2010," Available from: (http://news.sciencemag.org/sciencenow/2010/03/swine-flu-pandemic-reincarnates-.html?rss=1), Accessed on October 1, 2010

[2] Tokyo: Ministry of Health, Labor and Welfare, "Japan, Influenza A(H1N1)," Available from: (http://www.mhlw.go.jp/english/topics/influenza_a/index.html), Accessed on June 1, 2009

[3] Sistema Nacional de Vigilancia Epidemiolgica (SINAVE), Mexico City, "Mexico Ministry of Health," Available from: (http://www.dgepi.salud.gob.mx/sinave/index.htm.)

[4] H. Nishiura, C. Castillo-Chavez, M. Safan and G. Chowell, *Transmission potential of the new influenza A(H1N1) virus and its age-specificity in Japan,* Euro Surveill, **14** (2009), pii: 19227.

[5] V. Trifonov, H. Khiabanian, B. Greenbaum and R. Rabadan, *The origin of the recent swine influenza A(H1N1) virus infecting humans,* Euro Surveill, **14** (2009), pii=19193. Available from: (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19193)

[6] G. J. Smith, D. Vijaykrishna, J. Bahl, S. J. Lycett, M. Worobey, O. G. Pybus, S. K. Ma, C. L. Cheung, J. Raghwani, S. Bhatt, J. S. Peiris, Y. Guan and A. Rambaut, *Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic,* Nature, **459** (2009), 1122–1125.

[7] G. Chowell, S. M. Bertozzi, M. A. Colchero, H. Lopez-Gatell, C. Alpuche-Aranda, M. Hernandez and M. A. Miller, *Severe respiratory disease concurrent with the circulation of H1N1 influenza*, N. Engl. J. Med., **361** (2009), 674–679.

[8] J. Taubenberger and D. M. Morens, *1918 Influenza: The mother of all pandemics,* Emerging Infectious Diseases, **12** (2006), 15–22.

[9] G. Chowell, C. Viboud, L. Simonsen, M. A. Miller and R. Acuna-Soto, *Mortality patterns associated with the 1918 influenza pandemic in Mexico: evidence for a spring herald wave and lack of pre-existing immunity in older populations*, Journal of Infectious Diseases, **202** (2010), 567–575.

[10] M. A. Miller, C. Viboud, M. Balinska and L. Simonsen, *The signature features of influenza pandemics–implications for policy*, N. Engl. J. Med., **360** (2009), 2595–2598.

[11] W. W. Thompson, D. K. Shay, E. Weintraub, L. Brammer, N. Cox, L. J. Anderson and K. Fukuda, *Mortality associated with influenza and respiratory syncytial virus in the United States,* JAMA, **289** (2003), 179–186.

[12] S. Towers and Z. Feng, *Pandemic H1N1 influenza: predicting the course of a pandemic and assessing the efficacy of the planned vaccination programme in the United States,* Euro Surveill. **14** (2009), pii=19358. Available from: (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19358)

[13] R. Roos, "H1N1 Viruses Gain Tamiflu Resistance Without Losing Fitness," Center for Infectious Disease Research and Policy, University of Minnesota Available from: (http://www.cidrap.umn.edu/cidrap/content/influenza/panflu/news/mar0209osel.html) March 2, 2009

[14] M. Helferty, J. Vachon, J. Tarasuk, R. Rodin, J. Spika and L. Pelletier, *Incidence of hospital admissions and severe outcomes during the first and second waves of pandemic (H1N1) 2009*, Canadian Medical Association Journal.

[15] J. B. Plotkin, J. Dushoff and S. A. Levin, *Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus,* PNAS, **99** (2002), 6263–6268

[16] J. Lin, V. Andreasen, R. Casagrandi and S. A. Levin, *Traveling waves in a model of influenza a drift,* Journal of Theoretical Biology, **222** (2003), 437–445.