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Column Editor

Learning from the Past to Prepare for the Future: Modeling the Impact of Hypothetical Interventions During the Great Influenza Pandemic of 1918

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The Influenza Epidemic of 1918: Crowded sleeping area at the Naval Training Station, San Francisco, California

Courtesy of U.S. Naval Historical Center Photography

Recurrent outbreaks of avian H5N1 influenza (flu) in poultry and other birds in several regions around the world during the last few years have highlighted the need to prepare for the next influenza pandemic. Although most H5N1 flu cases in humans have been attributed to close contact with infected poultry, limited human-to-human transmission cannot be ruled out. Should this novel flu virus be able to recombine with existing human flu strains or mutate into a form that is capable of efficient human-to-human transmission, a pandemic of great magnitude could sweep the world.

Pandemics are global epidemics associated with a high morbidity and mortality burden. There have been four pandemic outbreaks in recent history: the Asiatic (Russian) flu (1889–90), the Spanish flu (1918–19), the Asian flu (1957–58), and the Hong Kong flu (1968–69). Some pandemics, such as the Asian flu outbreak, have been relatively minor and quickly contained; others, such as the Spanish flu, could not be contained.

The consequences of failing to contain a disease epidemic can be disastrous. It is estimated that at least 20 million deaths were due to the Spanish flu. One million deaths have been attributed to the Asian flu. In the United States, about 675,000 lives were lost to the Spanish flu with an approximate case fatality rate of 2%; that is, about 2% of flu cases succumbed to the disease. This case fatality rate is an order of magnitude larger than the case fatality rates observed in seasonal flu epidemics in normal years.

"Regular" epidemics of influenza, which occur annually in temperate regions of the world during the winter months, are no less of a threat. Influenza can be deadly, and it claims roughly 36,000 lives each year in the United States alone. The virus causing influenza has an antigenic structure that mutates frequently. Most of the time, the mutations are minor. These mutations ensure the persistence of the virus in populations that develop immunity against

Figure 1. One of the many newspaper highlights on the 1918 pandemic influenza in Geneva, Switzerland, announcing the end of the pandemic

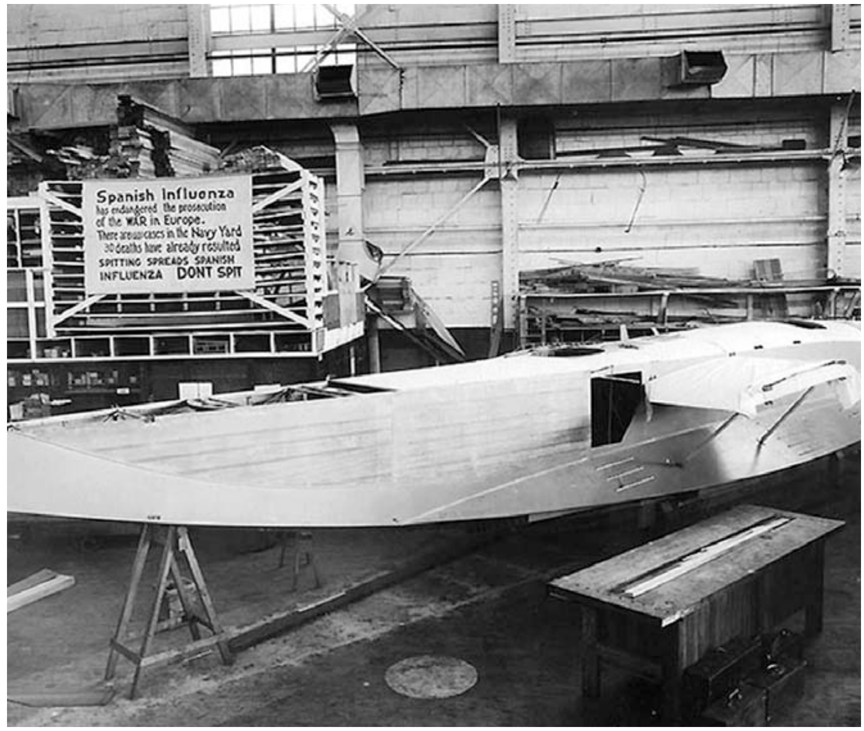
Courtesy: *La Suisse* (newspaper), February 01, 1919 individual virus strains. However, major changes in the virus composition can also occur, mainly from the recombination of different influenza viruses, especially those in waterfowl. This often results in novel influenza subtypes to which the human population has little or no immunity and which, in turn, lead to influenza pandemics. The severity of flu pandemics could depend on the population immunity background, the virus virulence, the human-to-human contact rate, and the effectiveness of control interventions.

Recently, scientists at the Armed Forces Institute of Pathology in Rockville, Maryland, reconstructed the virus from remains of victims of the 1918 pandemic preserved in the Alaskan permafrost. The reconstructed strain is an H1N1 virus, which likely originated from a bird flu. This virus strain and the emerging H5N1 avian flu virus both seem to kill via an overly vigorous response of the victims' immune systems ("cytokine storm"), according to Michael Osterholm, who wrote "Preparing for the Next Pandemic" for *The New England Journal of Medicine* in 2005.

The risk of a new bird flu pandemic is real, as is attested by the World Health Organization's warning of a substantial risk for an influenza pandemic outbreak over the next few years. This warning highlights the need to prepare for a potential pandemic event. Hence, understanding the effectiveness of the various intervention strategies available to decisionmakers is critical to ensuring epidemic control.

Simulations and mathematical models are important tools to help prepare for epidemic events by making it possible to evaluate the effectiveness of various intervention strategies. Interventions are varied, but they aim at the following:

- Reducing the contact rate of humans with poultry and birds in general by altering farming practices and banning cock fights
- Increasing public hygiene, such as the use of protective gear (e.g., face mask)
- Implementing isolation measures such as school closures, quarantine, effective isolation of infectious cases in hospitals
- Implementing pharmaceutical interventions that include the use of antiviral medications for both treatment and prophylaxis



F61 Aircraft Hall at the Naval Aircraft Factory, Philadelphia, Oct. 19, 1918

Courtesy of www.usasearch.gov

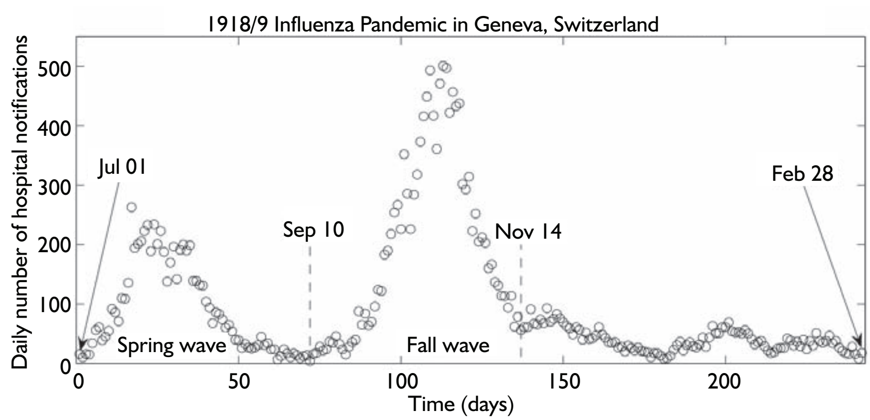


Figure 2. Daily number of hospital notifications of influenza cases during the 1918–1919 influenza pandemic in the Canton of Geneva, Switzerland

Thus, by modeling the 1918–1919 Spanish flu pandemic, we can evaluate the impact of hypothetical control interventions on morbidity and mortality, as well as on the duration and peak of the main wave of infection of a pending influenza pandemic.

The Spanish Flu Pandemic

The 1918 influenza pandemic is the most severe pandemic in recent history. While it is referred to as the "Spanish" flu because it was widely reported by the uncensored press of a nation not at war, this pandemic is thought to have originated not in Kansas and spread worldwide by mass movement of troops in the First World War. However, earlier accounts of a similar form of disease to the 1918 pandemic were reported in 1916–1917 at Etaples military camp in France, raising the possibility that a similar variant of the pandemic strain was already circulating prior to 1918. In fact, evidence indicates the elderly population

Figure 3. This picture shows a church service being held outdoors in Lausanne, Switzerland. Places of indoor assembly—including churches, theaters, and dance halls—were closed during the 1918 influenza pandemic as a measure to reduce transmission of the disease.

Courtesy: *La Patrie Suisse* (newspaper), August 21, 1918

Chinese pandemic flu: influenza patients by their beds. In July, an American soldier said that while influenza caused a heavy fever, it "usually only confines the patient to bed for a few days." The mutation of the virus changed all that.

Courtesy of www.usasearch.gov

was not as affected as young adults, probably due to partial protection they had acquired from a similar virus long before the 1918–1919 pandemic.

The 1918–1919 pandemic swept the world in a series of up to three waves of varying severity. The first pandemic wave took place around the spring and summer time. For example, the first wave ("herald" wave) reached France in March, England in June, and Switzerland in July 1918. The second wave ("fall" wave) was the most severe and occurred around October–November of 1918, whereas the third wave ("winter" wave) was of limited intensity. This winter wave is probably associated to the seasonal flu, and took place in late 1918 and early 1919. The symptoms experienced during the second wave were typically more severe than those of the first and third waves. Symptoms included high fever, coughing, a distinctive dark violet coloration of face and finger tips due to a lack of oxygen supply to the blood, and nose bleeding. The last two conditions are medically referred to as heliotrope cyanosis and epistaxis, respectively.

While summary statistics about each wave are generally available, only a few regions have detailed records documenting the day-to-day evolution of the epidemic (Figure 1).

Thanks to a mandatory notification of influenza hospitalizations in the Canton of Geneva in Switzerland, we were able to manually extract daily counts

Spanish flu patients standing next to their beds

Courtesy of www.usasearch.gov

of influenza hospitalizations from the notifications registry archives in Switzerland for the July 1918–February 1919 period (Figure 2). The data reveal that in the Canton of Geneva, the influenza pandemic affected more than 50% of the population.

The overall case fatality was about 4.2%, and was, surprisingly, at its highest in the 21–40 age group, particularly in males. These findings are consistent with the theory that the virus kills via a cytokine storm, a positive feedback loop between cytokines that stimulates excessive immune cell reactions and the production of more cytokines.

During the pandemic, control measures were implemented, but there is no evidence of their effectiveness because disruptions in the sanitary, medical, private, and public sectors were common. Although there were unsuccessful efforts to develop a vaccine known as protovaccination, neither an influenza vaccine nor an antiviral medication was available for prophylaxis or treatment in 1918. Moreover, the social climate was one of insecurity and fear, as the population questioned the effectiveness of the control measures that were undertaken, including school and church closures (Figure 3), banning public events and hospital visits, and mandatory spraying of disinfectants on the streets.

Mathematical Model of Influenza Transmission

Our data are the reported daily number of new hospitalizations. To model such data, classical mathematical epidemiology models classify individuals as either susceptible (S), infected and infectious (I), or recovered (R) and model the evolution of the number of individuals in each of these categories through a system of coupled differential equations (Figure 4). For a given set of initial conditions (initial number of susceptible, infected individuals) and epidemiological parameters (e.g., transmission rate, infectious period), these models can describe the expected course of an epidemic. The models can be extended by adding more "compartments" to better describe the dynamics of the disease, the impact of interventions, and variations in reporting rates depending on the severity of the disease. The underlying assumption behind these compartmental models is that the population is well mixed (i.e., that the average social distance—"degrees of physical separation"—between each pair of individuals is relatively short).

Influenza infection is characterized by a latent period of about two days, during which individuals are not able to infect others until they become infectious for a period lasting about four days. Some individuals become infected but remain subclinical, that is, they are either asymptomatic or develop only a mild reaction to the virus. Because these individuals are not directly observed as infected, it is difficult to quantify the burden of influenza in terms of number of cases. Nevertheless, our modeling of the dynamic evolution of the epidemic can uncover the fraction of subclinical cases because, once recovered, they become immune to further infections.

Because of the novelty of the 1918 influenza virus, we assume the entire population is susceptible at the onset of the pandemic. Anecdotal evidence supports our assumption that recovered individuals from the first (spring) wave in Geneva were immune to infection in the second (fall) wave. A percentage of individuals in the period of latency progress to the clinically infectious class, and the rest progresses to the asymptomatic class. As disruptions in the sanitary and medical sectors were common, hospitalized individuals were considered infectious in our model. Clinically infectious individuals were hospitalized or recovered without hospitalization (e.g., mild infections, hospital refusals). Hospitalized (reported) individuals either recovered or died from influenza. We also account for subclinical cases of influenza that showed mild symptoms or none at all (asymptomatic). Given that subclinical cases only shed a small amount of virus, their transmission rate is a fraction of that of clinical cases.

The above description translates into the compartmental model (Figure 4) for the transmission dynamics of pandemic influenza. This model places individuals in the following epidemiological categories: susceptible (S), exposed but not yet infectious (E), clinically ill and infectious (I), asymptomatic and partially infectious (A), hospitalized (H), recovered (R), and dead (D). We considered birth and natural death rates to have a common value (average life expectancy of 60 years in 1917). However, population demographics could have been neglected because the epidemic process occurred at a much faster time scale than births and deaths. Moreover, given the war, the Swiss soldiers stayed in their country to protect the border.

The parameters in this model are the transmission rate, recovery rate, diagnostic rate, relative infectiousness of asymptomatic cases, proportion of clinical cases, and initial numbers of exposed and infectious individuals. We estimated these parameters by minimizing the squared differences in the cumulative number of hospital notifications during the 1918 influenza pandemic in Geneva, Switzerland, to the values predicted by the model. The advantage of using the cumulative over the daily number of new notifications is that the former somewhat smoothes out known reporting delays on weekends and national holidays. However, using the daily curve of case notifications did not generate significant differences in parameter estimates. Figure 5 shows that there is a good agreement between the observed and fitted epidemic curves. Both the estimated variances of the parameters and sensitivity analysis confirmed the model was well fit by the data.

Our model predicts that most of the cases were either asymptomatic or experienced only mild infections. The fraction of symptomatic cases among infected individuals in the first wave was 10% and increased to 36% during the second wave. Our model also predicts that the fraction of symptomatic cases diagnosed in hospitals was about 60% for the spring wave and 83% for the fall wave. We explain these findings by noting that during the 1918–1919 pandemic, the number of sick people was such that some who did not warrant attention were refused admission in overcrowded hospitals.

Moreover, it is unlikely that individuals with mild symptoms sought medical attention. While misdiagnosis may be common for annual epidemics of influenza due to the limited reliability of clinical diagnosis (nonspecific symptoms), clinical diagnosis for pandemic influenza should be more reliable because of the severity of symptoms.

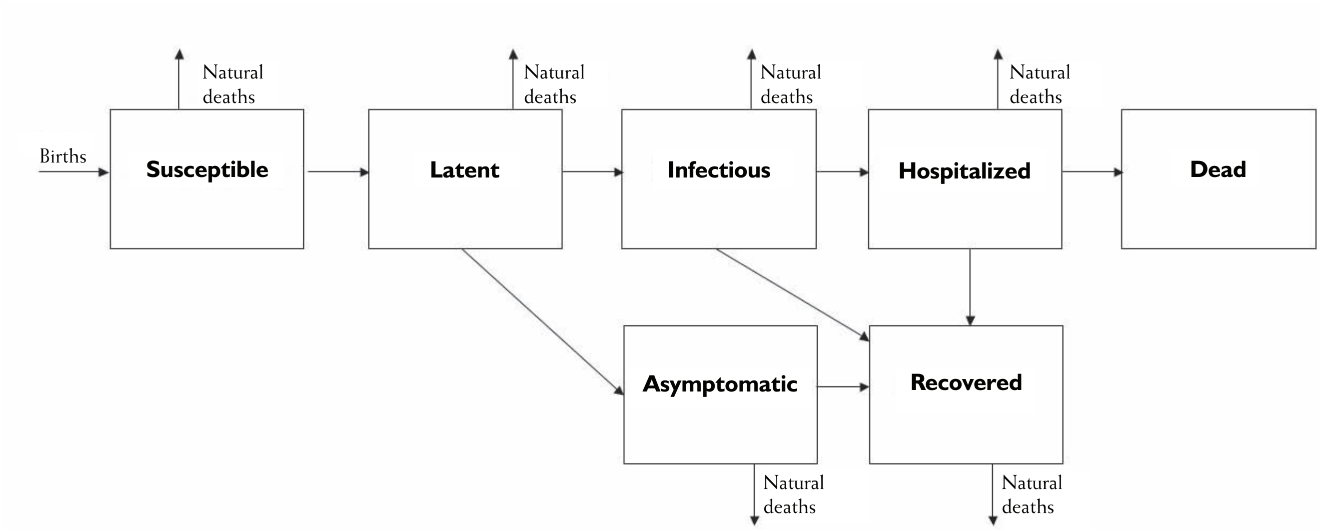


Figure 4. Schematic representation of the transition of individuals (indicated by arrows) among the different epidemiological states during an influenza pandemic

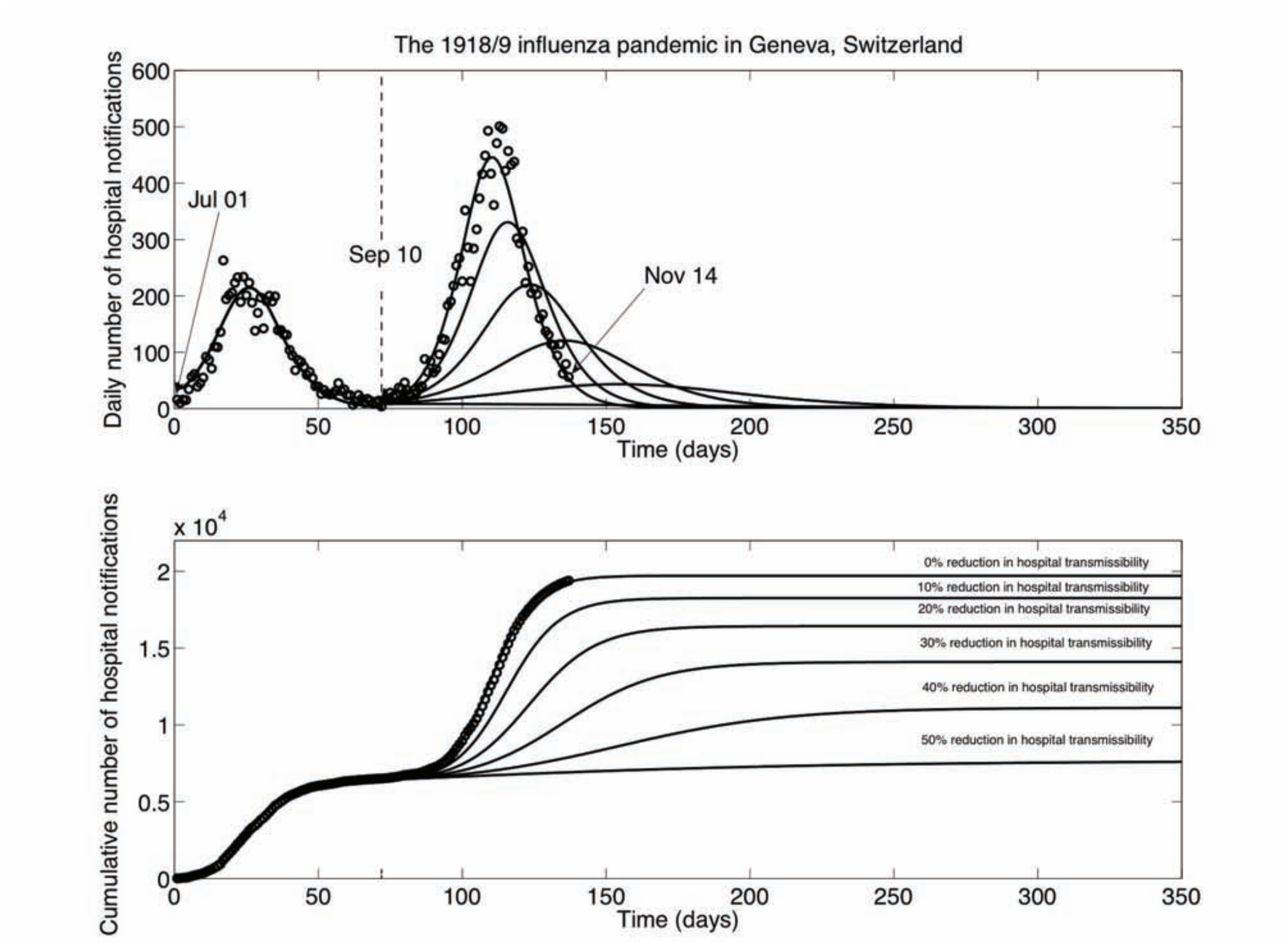


Figure 5. Model fit to the daily number of hospital notifications during the first two waves of the 1918 influenza pandemic in the Canton of Geneva, Switzerland, and the effects of reducing the transmission rate from 10% to 50% within hospital settings

Modeling Intervention Strategies

Compartmental models, such as the one we fit to data, can be used to investigate the impact of various intervention strategies. For example, we can quantify the effects of a reduction in the transmissibility of infectious cases in hospitals via effective isolation strategies through a reduction in the transmission rate of hospitalized infected individuals. Similarly, the impact of antiviral drugs, vaccination, and increased hygiene and protective measures (e.g., increased hand washing, use of face masks) can be quantified in a crude way through a change of transmissibility in the general population.

We explored the impact of hypothetical intervention strategies based on our modeling results from the historical data of the influenza pandemic in Geneva. Our numerical investigation supposes that the first herald wave served as a call for action, and, thus, at the onset of the second wave, intervention strategies were ready to be implemented. We evaluated the role of hypothetical reductions in the transmission rate of the population and reductions in the transmissibility of infectious individuals in hospital settings via improved isolation strategies during the second wave.

Figure 5 shows the effects of a reduction in the transmissibility of infectious individuals in hospitals during the fall wave through an improvement in effectiveness of isolation strategies. In fact, a 50% reduction in transmissibility from hospitalized cases would predict a significant reduction in the number of hospitalized cases. Although the resulting epidemic curves after the control intervention indicate a longer epidemic duration, the epidemic peak sizes are significantly reduced, which is beneficial for case management in hospital settings. The combination of effective isolation strategies in hospital settings and reductions in the transmission rate of the population lead to even greater reductions in morbidity and mortality, as shown in the supplementary material at *www.amstat.org/publications/chance.*

It should be noted that the Geneva influenza data were obtained during a rather difficult time and the course of the pandemic was subject to several unique factors such as war, disease, and food rationing. Factors that could affect the time course and containment of the next influenza pandemic include population demographics, highly connected transportation systems, and an improved public health system. However, these uncertainties are probably of smaller magnitude than the pathogenicity and virulence associated to the next influenza pandemic virus strain.

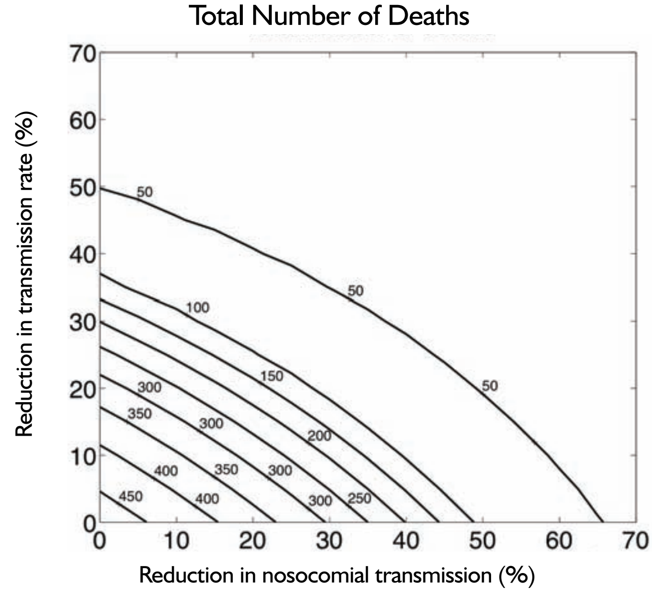


Figure 6. The combined effect of reductions in the transmission rate in the general population and reductions in transmissibility from hospital settings (nosocomial transmission) on the final number of deaths

Our approach is based on the calibration of a reasonable model of influenza transmission using retrospective epidemic data. We then explore different hypothetical "what if" scenarios by tuning in to appropriate model parameters. This allows us to explore, for example, the effectiveness of hypothetical control strategies in terms of final epidemic size, peak size, and duration. We have shown that mathematical models can be useful tools to increase our understanding of historical epidemics and guide public health officials in effectively planning and controlling future epidemics.

Further Reading

Ammon, C.E. (2002). "Spanish Flu Epidemic in 1918 in Geneva, Switzerland." *Euro-Surveillance*, 7:190–2.

Anderson, R.M., and May, R.M. (1999). "*Infectious Diseases of Humans.*" Oxford University Press: Oxford.

Castillo-Chavez, C. et al. (2003). "Mathematical Models of Isolation and Quarantine." *Journal of the American Medical Association*, 290:2876–2877.

Castillo-Chavez, C., Brauer, F. (2000). "*Mathematical Models in Population Biology and Epidemiology.*" Springer: New York.

Chowell, G., Ammon, C.E., Hengartner, N.W., Hyman, J.M. (2006). "Transmission Dynamics of the Great Influenza Pandemic of 1918 in Geneva, Switzerland: Assessing the Effects of Hypothetical Interventions." *Journal of Theoretical Biology*, 241:193–204.

Osterholm, M.T. (2005). "Preparing for the Next Pandemic." *The New England Journal of Medicine*, 352:1839–1842.

Taubenberger, J.K. et al. (2005). "Characterization of the 1918 Influenza Virus Polymerase Genes." *Nature*, 437:889–893.

Tumpey, T.M. et. al. (2005). "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus." *Science*, 310:77–80.

Oxford, J.S. et al. (2006). "Scientific Lessons from the First Influenza Pandemic of the 20th Century." *Vaccine*, 24:6742–6746.

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