Pandemic lessons from Iceland

Scott F. Dowell* and Joseph S. Bresee
Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30333

Pandemic influenza arrived in Iceland on October 19, 1918, and spread across the country with a speed and virulence that was typical of the so-called Spanish flu. The epidemiologic features of this pandemic are described by Gottfredsson *et al.* (1) in this issue of PNAS. These features, only now being described with precision some 90 years after the events, help to explain the unusual lethality of the historical epidemic and also highlight vulnerabilities that might be exploited for modern control measures. However, the most important contribution of the Gottfredsson *et al.* article is the detailed analysis of genetic susceptibility and their conclusion that family exposures outweighed genetics as risk factors for fatal influenza during this pandemic. This finding was made possible both because of the unique genealogical database that exists in Iceland and because the rapid spread of the disease across the island enabled the authors to identify pandemic deaths with relative precision.

The Iceland Epidemic

The 1918 pandemic of influenza moved across Iceland in only 42 days, a phenomenon more influenced by the very short serial interval of 4.1 days between generations of cases than by the transmissibility of the virus. Transmissibility, measured as the average number of individuals infected by each case, was modest at 2.2 for the Iceland epidemic, and mortality was 2.8% with a W-shaped age distribution curve. This is consistent with estimates from other countries (2–5) that have prompted speculation that similar viruses might be vulnerable to early containment (2, 6). During those 42 days, 521 Icelanders died, an increase of >500% from the comparable period of the year before. This unprecedented clustering of deaths in a short period also allowed the investigators to identify influenza-associated deaths with unusual precision, despite the lack of a specific diagnostic test in the previral era. Specificity in the identification of infected survivors was not equally possible, a point to remember when considering the accuracy of estimates of case/fatality proportions.

A more important implication of the modest transmissibility and short serial interval was that the rapidly moving epidemic was susceptible to public health measures, if they could be applied quickly enough. Where measures to reduce community spread were introduced in the northern and eastern parts of Iceland, there was apparent absence of disease. A systematic study of 43 U.S. cities (5) found that the isolation of ill cases, quarantine of close contacts, and community measures to decrease social contact (e.g., school closing) were significantly associated with lower mortality. Even so, the effect was often temporary, as in St. Louis and Denver, where second waves of infection were introduced from nearby geographic areas soon after the public health measures were lifted. Isolated in the North Atlantic Ocean, the northern and eastern parts of Iceland may have been spared a second wave, raising the possibility that similar interventions, if applied consistently and sustained long enough, could have more than a temporary effect in future settings. Many governments, including that of the United States (7), have developed plans for the use of community mitigation interventions designed to slow the spread and reduce attack rates during a pandemic. It is hoped that measures such as isolation of ill persons, quarantine of those exposed, closing of schools and businesses, travel restrictions, and other nonpharmaceutical interventions will be successful in delaying the peak of an epidemic, reducing the number of hospitalizations and deaths at its peak, and reducing the overall mortality.

The 1918 pandemic of influenza moved across Iceland in only 42 days.

One of the most frequently asked questions about the current epidemic of avian influenza A (H5N1), as well as about the 1918 pandemic, is whether a genetic predisposition explains the distinctive disease clustering within families. It is important to note that the two viruses are quite different: the 1918 virus was a true pandemic human pathogen, whereas H5N1 is primarily an animal pathogen with occasional human infections and clusters. Despite millions of exposures of people worldwide to poultry infected with the H5N1 virus, ≈330 human cases have been confirmed, and >95 of these have been part of family clusters (8). If the family clustering is primarily a product of common exposures or close contact with infected persons, it might be possible to reduce attack rates and mortality through interventions directed at reducing intrafamilial contact or otherwise protecting household members in close contact with an ill relative. Alternatively, if the risk of infection, or of serious disease once infected, is primarily related to genetic susceptibility, much more work will be needed to identify the genes responsible and explore future opportunities for modified vaccines or treatments.

The present Iceland analysis (1) takes a special opportunity to address the question of genetic susceptibility in a rigorous and systematic manner. Since 1703, the entire population of Iceland has been closely tracked, and the genetic relatedness of individual Icelanders in 1918 can be documented through the deCODE genealogical database. Not surprisingly, family members of the 1918 influenza victims were at elevated risk for dying from influenza themselves. In fact, those most closely related (siblings and parents) were at highest risk, and those more distantly related were at somewhat lower risk. However, the spouses of victims, often the only genetically unrelated member of the household, were paradoxically at the highest risk, prompting the investigators to duplicate the analysis for the relatives of the spouses. Their then-surprising finding was that relatives of spouses were at significantly elevated risk as well, and, with minor exceptions, the risks among relatives of the spouses mirrored the risks among relatives of the victims themselves.

Conflicting Results

A recently published paper (9) took a similar analytic approach using the Utah Population Database. The methods, and many of the results, were broadly similar to those of the Iceland investigation, but the conclusion appeared to be exactly the opposite–that there existed a heritable predisposition to death from influenza. Relatives of fatal influenza cases were at significantly

Author contributions: S.F.D. and J.S.B. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 1303.

*To whom correspondence should be addressed. E-mail: sdowell@cdc.gov.

increased risk for death from influenza, with relative risks (RRs) of 1.5 for first-degree relatives, 1.2 for second-degree relatives, and 1.2 for third-degree relatives, but again, the highest risk of all (2.0) was among spouses. Siblings of spouses were at significantly elevated risk as well (RR = 1.3), but their parents, grandparents, or third-degree relatives were not. An important influence on the authors' conclusion was the observation of increased risk among second- and third-degree relatives and their contention that such relatives share genetic material but not common environmental exposures.

What does this mean? Of course it is not the first time two groups of investigators have looked at similar results and drawn apparently opposite conclusions. Importantly, Gottfredsson *et al.* (1) conclude that genetic susceptibility was not in fact the major driver of increased family risk, which was also the conclusion reached in a recent analysis of H5N1 clusters (8) and which appears broadly consistent with observations from Utah that showed the highest risk for spouses and elevated risks also for the siblings of spouses (9). Presumably, if genetics was a factor at all in Iceland, it was greatly outweighed by close contact between family or household members, whether related or not, who either provided care for the ill family member or were otherwise exposed. There are at least two potential problems with this conclusion. First, we have no direct confirmatory information on the closeness of contact between the various relatives and the index family member dying of influenza, and presumably such information is no longer obtainable. Second, the increased risks presented were calculated for death from influenza, not for infection with influenza. If it is true that 65% of all Icelanders were infected—and we might assume that the proportion would be even higher in already affected households—then these elevated risks may approximate the risks for death given infection, rather than for infection *per se*.

An increased risk for death given infection for family members that is not related to genetic susceptibility would be an unusual, although not completely unprecedented, finding in infectious disease epidemiology. As the authors point out, there is some evidence that this might be the case for measles, where it has been attributed to higher inoculum size or repeated infections for those with closest contact or secondary household cases.

Another, perhaps simpler, explanation is that the increased risk for death among close relatives simply mirrors an increased risk for infection. If essentially all family members were infected, this could not be the case, but there are reasons to think that many may actually have avoided infection. The overall estimate of 65% of Icelanders infected may well be an overestimate because many conditions in addition to actual influenza infection produce influenza-like illness, especially as compared with the specificity of a characteristic death during the 42-day pandemic period. If this simpler explanation is true and the increased risks among family members are more related to increased intensities of exposures among the closest relatives and sparing of others, the implications for our current pandemic preparedness become more clear.

Modern Implications

Preventing deaths from pandemic influenza should, therefore, focus on preventing infections among family members, especially those close family members providing care or with the most exposure to the ill person. The conditions of exposure in a future pandemic may be closer to conditions in Iceland in 1918 than many might assume. An important component of the current pandemic planning strategies in the United States and many other countries is to keep ill persons out of the hospital and have large numbers of them cared for at home, with the idea of avoiding the amplification of infections in hospitals seen with SARS in 2003 and with a range of other modern epidemics (7).

Although sensible from an epidemiological perspective, such large-scale home treatment of seriously ill relatives is untested in the modern world. Efforts are under way to help families facing such a situation by providing guidance for home-based infection control procedures, limiting the caretaking responsibilities to one or as few relatives as possible, and other measures. However, the availability and distribution of personal protective equipment for caregivers, the use of antivirals for ill persons during a pandemic, the potential for antiviral prophylaxis of exposed household members, education about how to safely provide home care and when to seek advanced care at a medical facility, and other aspects of these recommendations, are in their infancy.

Taking advantage of the unprecedented swiftness and lethality of the 1918 epidemic and of hundreds of years of genealogic information in Iceland, Gottfredsson *et al.* (1) highlight close family exposures, rather than genetic susceptibility as the primary reason for the vulnerability of the closest relatives of the pandemic victims. It is clear from the opposite conclusions by a similarly strong group of investigators in Utah (9) that statements about the primacy of genetics or the environment should still be made with humility. In focusing our attention on intrafamilial exposures, Gottfredsson *et al.* highlight the need for current pandemic plans to focus more intensively on safe home treatment of pandemic influenza victims of the future.

1. Gottfredsson M, *et al.* (2008) Lessons from the past: Familial aggregation analysis of fatal pandemic influenza (Spanish flu) in Iceland in 1918. *Proc Natl Acad Sci USA* 105:1303–1308.
2. Mills CE, Robins JM, Lipsitch M (2004) Transmissibility of 1918 pandemic influenza. *Nature* 432:904–906.
3. Vynnycky E, Trindall A, Mangtani P (2007) Estimates of the reproduction numbers of Spanish influenza using morbidity data. *Int J Epidemiol* 36:881–889.
4. Viboud C, *et al.* (2006) Transmissibility and mortality impact of epidemic and pandemic influenza, with emphasis on the unusually deadly 1951 epidemic. *Vaccine* 24:6701–6707.
5. Markel H, *et al.* (2007) Nonpharmaceutical interventions implemented by US cities during the 1918–1919 influenza pandemic. *J Am Med Assoc* 298:644–654.
6. Longini IM, Jr, *et al.* (2005) Containing pandemic influenza at the source. *Science* 309:1083–1087.
7. Centers for Disease Control and Prevention (2007) *Interim Pre-Pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States—Early, Targeted, Layered use of Nonpharmaceutical Interventions*. Available at http://www.pandemicflu.gov/plan/community/community_mitigation.pdf.
8. Pitzer VE, Olsen SJ, Bergstrom CT, Dowell SF, Lipsitch M (2007) Little evidence for genetic susceptibility to influenza A (H5N1) from family clustering data. *Emerg Infect Dis* 13:1074–1076.
9. Albright FS, Orlando P, Pavia AT, Jackson GG, Albright LAC (2008) Evidence for a heritable predisposition to death due to influenza. *J Infect Dis* 197:18–24.