Pandemic influenza: Studying the lessons of history

Stephen S. Morse

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Pandemic influenza: Studying the lessons of history

Stephen S. Morse*

Department of Epidemiology and Center for Public Health Preparedness, Mailman School of Public Health, Columbia University, New York, NY 10032

Next year will mark the 90th anniversary of the great influenza pandemic of 1918, an event widely considered to be one of the greatest natural disasters in human history. Historians estimate that ≥50 million people died worldwide, including >450,000 documented deaths in the United States alone (1). Since then, the 20th century witnessed two more influenza pandemics, although fortunately none comparable in ferocity to the 1918 pandemic (2). Pandemics—epidemics so large that virtually the entire world is affected—have occurred several times in each of the last several centuries. Most virologists therefore believe that it is inevitable that we will experience at least one pandemic in this century, and very likely more. However, if a pandemic were to strike in the near future, it is likely that vaccine would not be available for at least 4–6 months (3). Antivirals, if effective against the pandemic strain, would probably also be in short supply. Few of these measures can be applied at pandemic scale, in which half the population of the world would likely be infected over the course of a year or more. We would be left with other measures, now termed "nonpharmaceutical interventions," to stave off the worst effects of a pandemic until a vaccine could be produced and widely administered (4, 5). Because many of these interventions, such as closing schools or shutting down mass transit, could be very disruptive to society, it is important to use effective measures in a rational way. But which measures are most effective, and how should they be applied? Do any nonpharmaceutical interventions actually help? Until now, there has been very little systematic examination of these questions. However, different U.S. cities showed marked differences in influenza attack rates and mortality in 1918. Some cities, St. Louis for example, appeared to have weathered the pandemic with far fewer excess deaths than others (6, 7). What distinguished the severely afflicted cities from those that were less heavily stricken? As it happens, different cities took different approaches to implementing interventions. These differences constituted natural experiments and offer an opportunity to address important questions concerning nonpharmaceutical interventions by using the historical data. In this issue of PNAS, Hatchett *et al.* (6) and Bootsma and Ferguson (7) have made important contributions to our understanding of these questions by using the historical data approach to examine the effects of various interventions used during the 1918 pandemic.

Nonpharmaceutical Interventions in 1918

A variety of interventions were available in 1918, from wearing surgical masks to "social distancing" measures (as we call them today) that ranged from closing schools and prohibiting public gatherings to isolating sick people in hospitals or encouraging them to stay home. Most of the interventions then available are identical to the measures that would be considered today (8). Both articles reach similar conclusions, using complementary methods.

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In the 1918 pandemic, no single intervention was sufficient, although some interventions were more useful than others. As might be expected for a respiratory infection, closing schools, churches, and theaters, for example, appeared to be among the most effective measures. Four or more such interventions implemented at the same time were more effective than only one or two and were more effective than multiple interventions started at different times (6). Of course, this activity might also be a proxy for how seriously a city viewed the pandemic. Nevertheless, there were significant differences. Timing was especially critical. Both articles demonstrate that these measures were far more effective if applied early and maintained as long as possible. Cities that put several measures in place early (before the cumulative excess death rate reached ≈20–30/100,000 population) experienced peak death rates that were approximately half of those seen in cities that started their interventions later. The authors note that few cities maintained the interventions for >6 weeks, approximately the time it took for one wave of the pandemic to pass through the area. Influenza returned when the interventions were relaxed. Pandemics have tended to come in waves, so a city could implement effective measures and avoid the first wave, only to relax them and be hit by the next. Bootsma and Ferguson (7), in fact, make the interesting argument that escaping the pandemic entirely may not be the most advantageous strategy because it only leaves everyone susceptible to infection later. How does one keep up the necessary caution for what may be months or longer? Experiences from 1918 suggest that it was possible to get reasonable compliance with precautionary measures for a while, but not indefinitely, even in the more obedient social climate that prevailed in 1918. San Francisco had demonstrations in which citizens defiantly tore off their own masks (9). Obtaining long-term compliance is likely to be even more difficult today, although there was a relatively high level of public compliance with recommended infection control measures during the severe acute respiratory syndrome (SARS) epidemic in Toronto. These experiences suggest that, although it is difficult to maintain compliance, it is not impossible.

Despite the difficulties, nonpharmaceutical interventions can fulfill lifesaving objectives. Spreading out the peak of infection over a longer period of time could reduce the burden on healthcare institutions and essential services. A chief purpose of nonpharmaceutical interventions today would be to reduce the effects of the pandemic as much as possible until vaccine could be produced and administered. In that case, people might be more willing to accept these precautions for several months, knowing that eventually the restrictions would end. Hope is a strong inducement.

Are We Better Off Today?

These considerations have direct relevance to our concerns today. The findings of Hatchett *et al.* (6) and Bootsma and Ferguson (7) support the general idea of "social distancing" that is the keystone of

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*E-mail: ssm20@columbia.edu.

current nonpharmaceutical intervention strategies and indicate that some interventions were probably of little value. As with any historical data, extrapolations to the present must be made with caution. There are significant social and technological differences between 1918 and today. In today's increasingly globalized world, when we can circumnavigate the planet within the incubation period of an influenza infection, can the pandemic be spotted and the right interventions applied in time to be effective? This question emphasizes the critical need for effective surveillance and response. However, the work at hand does provide some cause for limited optimism, suggesting that, even at today's rapid pace, if a city acts quickly it can buy time even when the pandemic appears at its gates. Another difference between 1918 and now is the increasing urbanization, which also makes more of the world vulnerable. In the earlier years of the 20th century, there were far greater differences between urban and rural areas. Since then, cities have grown larger, more numerous, and more densely packed with inhabitants. Far more commonly than in 1918, many people commute daily to large cities. Finally, there are differences in the makeup of the household, with increasing numbers being headed by single parents or having both parents working. Closing schools would be far more burdensome for many in our current setting than it was in 1918.

To be sure, we do have a number of advantages over 1918. Some of the victims then may have been carried off by secondary bacterial infections that might be treatable today. Antiviral medications may also be available, and for those of the sickest patients who have access to intensive care, ventilators might save more lives. Infection control measures are somewhat better, too, at least for healthcare workers, with more effective respiratory protection. But most of all, one hopes that vaccine could become rapidly available. Since the 1950s, vaccines have been the definitive strategy for combating influenza epidemics, and this is unlikely to change in the foreseeable future. Even with only enough vaccine for part of the population, and imperfect distribution, "herd immunity" can have a considerable protective effect if sufficient vaccine can be administered in time (10). But under current circumstances, with global vaccine capacity severely limited (11), it may well require a pandemic to see whether this is even a realistic hope. The state of the world's vaccine capacity is deplorable and sorely in need of improvement. Even worse, with only a handful of countries that produce vaccines, the suffering could be exacerbated by regional socioeconomic inequities in distribution (12), a concern recently underscored by Indonesia's objections to providing new virus samples to the World Health Organization.

Progress and Paradox

The history of the 1918 pandemic also leaves us with some unresolved paradoxes. We have made great progress in characterizing the influenza virus and even crucial aspects of its pathogenesis. In recent years, the 1918 virus itself has been pieced together from painstakingly assembled portions of viral RNA sequences (13), and reasons for the unusual virulence of the virus are beginning to be unraveled (14). Despite the many years that have passed since 1918, however, there is much about the transmission, stability, and epidemiology of influenza that is still very poorly understood (5). One frustrating apparent paradox is the difficulty of reducing spread effectively. The work by Bootsma and Ferguson (7) utilizes the classic transmission model so effectively elaborated by Anderson and May (15). A key parameter in the model is R_0, the basic reproductive rate of the infection, which essentially states how many susceptible individuals each infected person would (on the average) infect. Thus, any infection with $R_0 < 1$ would sputter out quickly. Calculations by the present authors and others suggest that R_0 was ≈ 2 for the 1918 pandemic. Although exponential growth by powers of 2—the ultimate consequence of $R_0 = 2$—can be expected to give large numbers of cases if unchecked, it is perhaps surprising that the panoply of measures designed to interrupt transmission was still insufficient to bring R below 1, which would seem to require a reduction in transmission of only $\approx 60\%$.

Learning from History

That the historical data from 1918 still have such great utility today is both a demonstration of the value of history and a great irony in itself. The irony is that now, almost 90 years after the worst pandemic in recorded history, we still have so little understanding of many fundamental aspects of influenza transmission that we must rely on empirical results almost a century old. Clearly, much more research is needed to better understand influenza epidemiology and transmission, to design useful interventions, and to develop the technology to produce the necessary vaccines rapidly and in quantity.

Even with a thorough understanding of these issues, however, historical data can clearly offer valuable insights that are highly relevant to today's concerns—insights that in some cases can be obtained in no other way. Some have used the term "clioepidemiology" (after Clio, the muse of history) to refer to the mining and reanalysis of this rich store of often-neglected historical information (16). As these articles show, there is an invaluable treasure trove of useful historical data that has only just begun to be used to inform our actions. The lessons of 1918, if well heeded, might help us to avoid repeating the same history today.

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