
GINA KOLATA

Flu: The Story of the Great Influenza Pandemic of 1918 and the Search for the Virus That Caused It

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The most deadly epidemic of the twentieth century killed between 20 million and 40 million people, even more by some estimates. To put this toll in perspective, consider that combat deaths in the two world wars combined were about 28 million. The epidemic took the lives of healthy middle-aged individuals, males more than females. It killed in developing and developed regions alike. And the 1918 influenza pandemic remains one of the most enigmatic events in the history of disease. It is sometimes called the “Spanish” flu, probably because neutral Spain did not censor newspapers during the 1914–18 world war and hence covered the

flu's progress, but it appears not to have had a Spanish origin. An epidemic that left no corner of the world untouched, the 1918 influenza should be of great interest to readers of this journal, in spite of the fact that the topic has not preoccupied demographers. The epidemic per se is not the main subject of Gina Kolata's interesting and very readable book. Her concentration is on the ongoing search for clues as to why it was so peculiar and deadly. The epidemic is noted not only for its overall lethality, but also for high death rates at middle age, as opposed to the extremes of the age spectrum, as is normal for influenza. The 1918 death toll would correspond to at least 65 million deaths today, assuming the same percentage death rate. From the perspectives of historical interest and damage-limitation in the event of a recurrence, there remains much to be understood about the origins of the epidemic.

The book begins with a brisk summary of the epidemiology and human costs of the influenza in 1918. The focus here is the United States, although other regions are touched upon also. All the important aspects of the epidemic are discussed, including the rapidity of spread of the influenza and the rapidity of disease progression among those who were stricken, as well as the aforementioned lethality. The human side of the suffering is well illustrated with several vignettes.

The next chapter, "A history of disease and death," is a whirlwind introduction to some basics of what we know about infectious disease generally, and how we have come to know it. Kolata does a good job of mixing advances in knowledge with brief glimpses of the scientists involved. Covered here are the Black Death; cholera and John Snow; *Vibrio cholerae* and Robert Koch; and other stories. This will be familiar territory for many. At the end of the chapter, Kolata picks up a thread that is one of the most perplexing aspects of the epidemic: that it was generally forgotten in the American collective consciousness. Interestingly, she notes (p. 45) that nineteenth-century Britain also was eager to forget about its worst cholera epidemic.

Kolata then turns to the core subject of the book, science's efforts to understand what happened in 1918. She covers experiments, fruitful and otherwise, on humans, swine, and ferrets that led, eventually, to the knowledge that the 1918 flu was not caused by bacteria as had been thought, but by a virus (as is, indeed, all influenza). Blind alleys, such as theories that virus-bacteria co-infections accounted for the virulence, are discussed along with the successes, conveying what a puzzle the pandemic was and continues to be. Early on, a relationship between swine flu and the 1918 flu was established, and though this relationship stands up to modern genetic analysis, it is still not clear whether hogs are to blame for the events of 1918. The appearance of a swine flu strain in humans in 1976, however, created the fear of a repeat of 1918.

Anyone with an interest in health policy who is not already well versed in the particulars of the 1976 swine flu scare will enjoy reading Kolata's treatment of this episode. It is a fascinating case study of decision under uncertainty. Millions of Americans were vaccinated to prevent an epidemic that never happened, though a few early warning signs did exist. Vaccine side effects, both genuine and the result of coincidence, became the Achilles heel of the vaccination campaign, and it was called off. This is a cautionary tale, worth remembering. As opposed to vaccine programs that slowly cover the population by vaccinating everyone at a cer-

tain age (first birthday, for example), a national campaign to prevent another 1918-style outbreak must cover nearly everyone simultaneously. With so many being vaccinated in so short a time, many “ordinary” ailments, mild or serious, become associated with the vaccination just because they arrive sometime after vaccination. The ensuing catch-22 comes out very clearly: don’t vaccinate, and risk a catastrophe; or do vaccinate and guarantee, in the absence of an epidemic, a public relations nightmare. Of course, a successful vaccination campaign can thwart an epidemic before it happens, so even if vaccination had been warranted, it may appear, spuriously, that there was nothing to fear. The (ex-post) consensus in the 1976 case is that there was no latent epidemic to be prevented, and that the decision to vaccinate everyone was made too hastily. However, Kolata’s reluctance to paint the path taken as obviously wrong, simply because we now know the outcome (p. 122), is refreshing.

The swine flu scare is a reminder of the 1918 epidemic’s long shadow, a theme of the book. Without the sort of knowledge being pursued by the scientists profiled in *Flu*, we risk being unarmed when the next great flu pandemic arrives. How close are we to another pandemic? We were too close for comfort in 1997, when the Hong Kong bird flu episode provided another example of a zoonosis (pathogen transmission from animal to human). A boy in Hong Kong became sick with flu, later typed as an avian strain, and died. Then came more cases and six more deaths. Epidemiology comes out of the 1997 story less bruised than in 1976. In the end, the local reservoir of this emergent strain of animal virus was eliminated by the slaughter and disposal of over one million chickens. No pandemic was unleashed, but the search for clues from 1918 went on.

The book’s greatest strength is the way it profiles the personalities behind the science. Jeffrey Taubenberger of the Armed Forces Institute of Pathology in Washington, DC was inspired one day in 1995 when he read a study using the new technique polymerase chain reaction (PCR). This technique amplifies the most minute traces of genetic material, so that large enough samples can be made to permit genetic decoding, called sequencing. Taubenberger wanted to do his own study using PCR, something that would make a splash—and he had access to thousands of historical tissue samples, preserved and embedded in paraffin, courtesy of his job at the Institute. Brainstorming with his colleagues, he hit upon the idea of investigating samples from victims of the 1918 flu. With Ann Reid and other colleagues, he succeeded in extracting viral genetic material, and sequenced parts of the viral genome. Johan Hultin, a Swedish-born pathologist whose adventurous life is profiled by Kolata, also provided Taubenberger with samples, whose sequences were used to validate the original findings.

Hultin is one of the most important medical detectives of the 1918 influenza, and Kolata does justice to his story. In 1951—long before PCR was invented—Hultin had an idea similar to Taubenberger’s. Eskimos were especially severely hit by the 1918 flu, and many died. Hultin went to Alaska and, with permission, dug in a mass grave of flu victims buried in the permafrost and obtained tissue samples. Back at his lab at the University of Iowa, he tried unsuccessfully to culture the flu virus. The viral genetic material was there, but the virus itself was dead. This was before the molecular biology revolution, and without the ability to grow live virus the result was nothing. And like so many negative results, it was never published.

But Hultin did not forget, and in 1997 he returned to the same gravesite and, without fanfare or outside funding, got new samples.

Another chapter discusses a much-publicized parallel effort to recover information about 1918 flu victims from bodies preserved in permafrost, this time in Spitsbergen, the Norwegian island in the Svalbard archipelago in the Arctic Ocean. This effort had the more ambitious goal of recapturing live 1918-type influenza virus, as opposed to collecting only genetic material to be sequenced. Having live virus would enable scientists to study the viral proteins. The structure of the proteins—which enables the virus to do its stuff—is determined by the code of the genetic sequence. However, because of the “protein-folding problem” (the solution of which is one of the current Holy Grails of molecular biology), knowledge of a gene sequence does not reveal everything about the corresponding protein structure. Success at recovering live virus would also pose a major security risk. In the end, the mission was a failure. The bodies in question were buried in the active layer of the permafrost. Exposed to freeze–thaw cycles every year, the corpses decomposed, scotching any chance that live virus would have survived.

These are human-centered stories, and Kolata gives a good sense of the scientists’ characters and provides glimpses into their workaday lives, and into the moments when an idea flashes by and becomes an obsession. Some may find too much of the “eureka!” aspect of science coming through, but I did not feel that this was emphasized unduly. Perhaps most of science is about slow and steady progress, but this story is one of scientists with insight and élan.

At the end of the book, Kolata reviews current theories about the epidemic. The gene sequencing done to date has provided hints as to the origin of the virulence of the 1918 flu, but not the smoking gun that had been hoped for. The prospects of another pandemic of hyper-virulent influenza are very real, though it is impossible to predict when it might occur. This is an ongoing story. After Kolata’s book came out, Taubenberger’s group published another 1918 gene sequence. Scientists will keep working on this puzzle. The stakes are too high not to.

The book is not without shortcomings. While a full-blown treatment of the biology of influenza is wisely left out, Kolata misses some opportunities to summarize other discoveries from influenza virology. For example, the finding by Bullough et al. (1994) that influenza virus undergoes a conformational change at the pH of membrane fusion—in other words, that the influenza virus has a sheathed harpoon that becomes unsheathed at the moment of entry into a host cell—is not mentioned. This would be of interest to readers of the book, because it shows how the flu virus gains entry to human cells via spectacular sub-microscopic cloak and dagger. *Flu* discusses the influenza hemagglutinin protein, and it would have been easy to include this.

In several places, Kolata touches on an analysis of why America was so intent on burying the memory of the 1918 flu, but she never wholeheartedly returns to this question. This social mystery parallels the scientific mystery of how the virus came to be so virulent, but in some sense it is harder to decipher. We may someday know, at a precise molecular level, why the 1918 flu virus caused such a severe epidemic. Kolata can hardly be held accountable for the fact that the social mystery will never be explained with the same precision, but it would have been rewarding to read some more on this aspect of the epidemic.

Like a good mystery writer, at key passages Kolata is careful not to reveal more information than was possessed by those she is describing. On page 62, for example, she discusses the perplexing spread of the epidemic, which seemed to cover some distances quickly and others slowly. This puzzle is still not understood completely, but, again, a more thorough return to this question would have been welcome.

A few other concerns can be raised. Kolata's speculation that influenza cannot be ruled out as the etiology of the Athenian plague of 431 BC (p. 37) is at odds with my reading of Thucydides' nosography. The consideration, on p. 197, of viruses and cancer curiously omits mention of the hepatitis-liver cancer nexus. These snags do not weigh down the overall experience, however. Disease is a big topic, and knowing when to bring in an interesting sidebar and when to stay focused on 1918 would be a tough job for any writer; Kolata does as well as anyone could in making these choices.

In many ways, *Flu* picks up where Alfred Crosby's definitive *America's Forgotten Pandemic* leaves off. Reissued in 1989, Crosby's book was originally published in 1976 (under the title *Epidemic and Peace, 1918*), and there has been enough progress in knowledge since the mid-1970s to provide ample material for a new book. Those who have not read Crosby's book but would like to learn more about the 1918 epidemic could profitably read his book and Kolata's, in either order. Those who have read Crosby's book will find Kolata's work a valuable update, though the first parts of *Flu* will be review. Readers who have kept pace with the recent work on the history and genetics of the epidemic, in the pages of *Science* and elsewhere, will find little new in this book beyond the human stories. In fairness, though, Kolata's intended audience is the broader science-interested public.

Kolata's day job is as a science reporter at the *New York Times*, and she writes with enviable clarity and style. This makes *Flu* enjoyable and educational reading. Those with any curiosity about the 1918 epidemic will find *Flu* worthwhile, while those with a potentially more serious interest in the subject will find it an excellent point-of-departure.

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