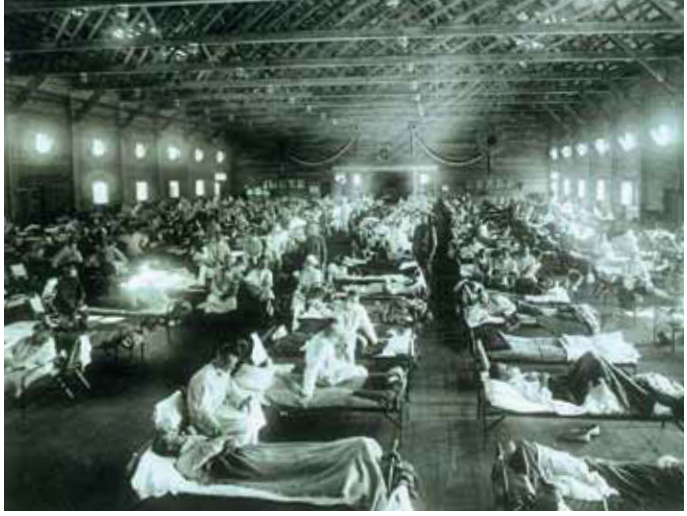


Deadliest Catch

Elusive, evolving flu difficult to predict

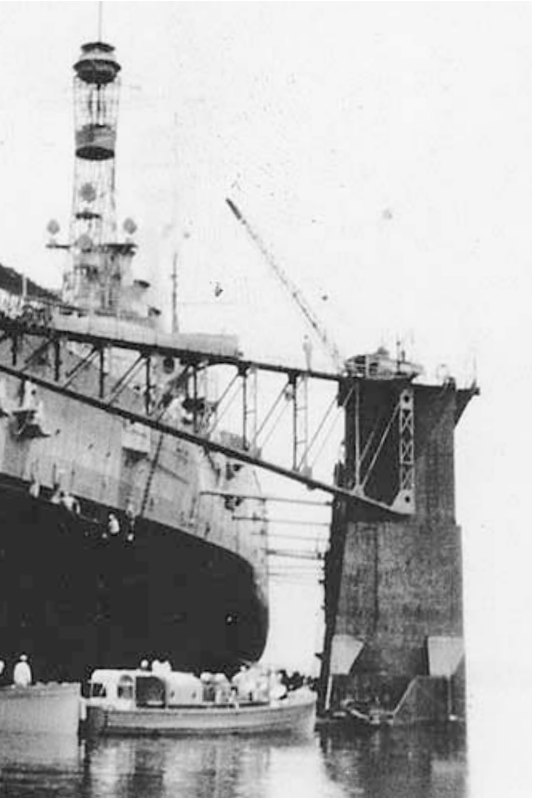
By Claudia S. Copeland, PhD

The year was 1918, and the world was reeling from a new, lethal strain of influenza. Fueled by wartime conditions, the deadly disease spread from country to country, the epidemic soon turning into a pandemic that by mid-summer had laid waste to soldiers across the European battlefields and beyond. Then, in mid-September, an oil-tanker with sick and dead crew members docked in New Orleans. The ship was immediately quarantined and the sick treated at a local hospital. Three days later, though, a United Fruit Company ship arrived with 11 more patients on board. With constant arrivals into this busy international port, it was impossible to contain the virus. Ten days after the first influenza patients had disembarked in the city, the first local case had been identified–the deadly Spanish Flu, as it was known, had hit New Orleans.

The USS Pittsburgh, one of many ships which harbored a deadly strain of Spanish Influenza on board, sickening 663 sailors (80% of the crew) and killing 58 of them in the Fall of 1918.

IMAGES COURTESY OF (TOP) U.S. NAVAL HISTORY AND HERITAGE COMMAND, (CENTER) NATIONAL MUSEUM OF HEALTH AND MEDICINE, ARMED FORCES INSTITUTE OF PATHOLOGY, WASHINGTON, D.C., UNITED STATES, (BOTTOM) COURTESY OF LIEUTENANT COMMANDER ELLIS M. ZACHARIAS, USN, 1931, U.S. NAVAL HISTORICAL CENTER.

A magnifired view of the H1N1 virus.



Once the virus began spreading within the New Orleans population, the epidemic erupted, leaving no one unaffected. In spite of a massive response on multiple levels—from the arrival of hundreds of volunteer Red Cross nurses to impressive cooperation between government agencies—one month after the first ship had arrived, over 2,000 cases per day were being reported. By the time it had run its course, almost 3,500 New Orleanians had died from the disease and countless others were severely affected. (A staggering 54,089 cases were reported in New Orleans between October 1918 and April 1919). Worldwide, mortality estimates range from 20 million to 100 million dead by the end of the pandemic, about a twentieth of the world's population at the time.

How could influenza, the same virus responsible for the humble seasonal flu, cause such a deadly epidemic? While the answer lies partly in the resources available in 1918 vs. today (such as antibiotics to fight secondary, bacterial infections), the virus itself was extremely aggressive, inducing an over-reaction of the immune system that led to acute respiratory distress syndrome, massive hemorrhaging of the lungs, and rapid fatality in previously healthy, young adults. The emergence of such a virulent virus from the backdrop of milder strains lies in the flu virus' dramatic, built-in ability to reinvent itself. Influenza accelerates genetic change through mixing genetic material from two or more viruses in a process called reassortment. The genome is divided into eight separate segments, and whenever natural hosts (primarily wild birds) are infected with more than one virus, segments from one viral strain can be packaged together with segments from another strain, essentially creating a new virus. That's why seasonal flu vaccination is required each year.

Public health virologists monitor newly emerging viruses and make their best judgment of which viruses will be the most problematic for humans. They then create a vaccine that protects against the top 3 or 4 of these. (In the future, this may not be necessary. Sridhar et al., in this September's *Nature Medicine*, unveiled a theoretical framework for a "universal influenza vaccine" based on T-cell responses to the core of the virus rather than antibody responses to surface proteins. The development of a real-world universal vaccine, however, will require years, if not decades, of development. Until

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INFLUENZA IS NOT A COLD; IT LASTS UP TO 2 WEEKS, WITH **SEVERE FATIGUE, FEVER, HEADACHES, AND MUSCLE ACHES.**

that far, theoretical point in the future, we will need to continue with the current system of getting a new flu vaccine each year.)

Vaccination is important. Even "regular," seasonal flu is deadly; each year, several thousand U.S. residents die of influenza. While deaths are generally confined to the elderly, the very young, and patients with certain chronic health conditions, when healthy people contract the flu it is no fun either. Influenza is not a cold; it lasts up to 2 weeks, with severe fatigue, fever, headaches, and muscle aches.

Getting vaccinated in Louisiana is easy; in addition to doctors' offices, many pharmacies offer vaccination on a drop-in basis. Since seasonal flu virus infections follow a pattern of gradually increasing in late Fall, peaking around the end of the year, and then diminishing through early spring, the recommended time for vaccination is in the early Fall, or as early as possible after that.

In Louisiana, influenza activity generally follows this pattern well. For example, last year's flu season (2012-2013) saw a gradual increase in flu cases starting around the beginning of October, until cases peaked around late December/early January, followed by a gradual decline until the end of spring. However, two seasons showed a remarkably different pattern here. In 2008-2009 and again in 2010-2011, there was a sharp spike in flu cases in August/September, and, in general, the flu cases in 2009 far outnumbered those of other years. This corresponded to the year when a pandemic of a different type of influenza virus, H1N1-2009, swept across Mexico, the United States, and, eventually, over 200 other countries.

The distinctiveness of the H1N1-2009 genome sequence is remarkable: 27.2% different from its predecessor, the 2008 "seasonal flu" strain of H1N1, and 6.1% different from the closest known influenza virus in nature. Its genome is a prime example of the power of reassortment, with elements of American and European swine influenza strains as well as avian and human strains. This deadly combination, particularly severe for pregnant women, resulted in over 18,000 deaths by May of 2010, according to the World Health Organization (WHO). In New Orleans, as elsewhere, children were hit hard by the virus. Children's Hospital was burdened with over 150 cases that required hospitalization, 3 deaths, and one boy who struggled for almost 500 days there, eventually requiring a kidney transplant. At this point in time, the pandemic seems to have crested, though cases continue to be seen, including a large outbreak in Venezuela last May that infected 250 people and killed 17. This season's vaccine (2013-2014) also includes an H1N1-like virus designed to protect against this strain of influenza.

In addition to H1N1-2009, two other non-seasonal influenza strains are currently of concern. The first, H7N9, is an avian flu associated with poultry in China, first reported in April of this year. The symptoms of this influenza strain are particularly severe; as of July 20, 2013, out of 134 cases of H7N9 reported in humans, 46 resulted in death. No human-to-human transmission has been seen, however. Chinese officials have taken action to contain the virus, including the closure of live bird markets, and the number of new cases has declined. No cases have been detected outside of China, but the Centers for Disease (CDC) is monitoring this virus closely because of the severity of the disease.

The other emerging strain of concern is H3N2v. This strain normally circulates in pigs, but has also infected humans, and has shown limited human-to-human spread. No sustained community spread has been seen, however, and most of the U.S. infections have been associated with prolonged exposure to pigs at agricultural fairs. Symptoms are similar to those of seasonal flu.

Of course, in states like Louisiana, the popularity of waterfowl hunting may present another source of new influenza strains– direct infection of hunters with wild-bird viruses. Louisiana hosts the largest harvest of wild birds in the USA. University of Georgia researchers Dorea et al. explored the possibility of a new viral strain emerging through reassortment between a human

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flu virus and a wild-bird avian influenza virus (AIV) contracted during hunting (or biological collection) activities. While antibody evidence clearly shows that hunters do get infected with AIV, the authors concluded that, due to the fact that seasonal human influenza and AIV are active at different times of the year here, it is unlikely that such recombination would occur. However, the season of peak activity of the H1N1-2009 virus in Louisiana did coincide with that of AIV in wild birds, making reassortment between these two strains possible in unvaccinated hunters or ornithologists.

So, if flu viruses are constantly developing new strains via reassortment, is it just a matter of time before a severe pandemic like the 1918 flu sweeps through the world again? A few epidemiological clues provide hints of the likelihood of such an outbreak. First, whereas the seasonal flu is more severe in vulnerable patients with weaker immune systems, the 1918 flu preferentially affected healthy individuals with strong immune systems; half of the victims were in their 20s and 30s. (Research done with reconstructed 1918 influenza virus supports an over-reaction by the immune system itself as the cause of most of the fatalities.) A pattern of human-to-human transmission preferentially affecting healthy individuals with robust immune systems would serve as a stark warning sign. This is not the pattern seen for H7N9 and H3N2v. For the H1N1-2009 pandemic, however, this was somewhat true; individuals aged 24 and younger were 15 to 20 times as likely as those over 65 to get sick with this virus, according to the CDC.

Second, the 1918 flu likely originated in a Kansas farming community, where pigs, birds, and humans lived in close proximity, that was located near a large army base. The base, Camp Funston, housed over 50,000 troops, and people regularly traveled between the rural community and the base, exposing a farm-origin virus to a large, crowded population. The new virus was then able to not only spread through this large, tightly packed population of soldiers, but was also regularly exported out as troops moved to different army bases in the U.S. and were deployed to Europe. This 'perfect storm' scenario is not likely to be repeated in the contemporary developed world. With today's communication and public health systems in place, an outbreak this severe, in circumstances like these, would be noticed and acted upon much earlier.

Third, the conditions of war most certainly had a large impact on the evolution of the virus. Normal, peacetime conditions favor the evolution of mild viruses, since people with severe illness tend to stay home, and therefore isolated, whereas those with mild illness tend to go to work or elsewhere where they mingle with, and infect, other people. Therefore, viruses causing mild illness have a selective advantage over those that cause severe illness. Under wartime conditions, however, those with mild illness will tend to stay outside, whereas those with severe illness will be crowded together in field hospitals, ideal places for the spread of influenza. Conditions in contemporary Louisiana therefore favor mild strains of influenza. On the other hand, virulent strains might be selected for in regions of the world currently experiencing war or upheaval. The speed of modern transportation and general mobility of the global population make it entirely possible that such strains could then be transported far and wide. After all, it was not the war itself, but simply cargo ships arriving from afar that brought the 1918 influenza epidemic to New Orleans that long-ago, ill-fated September. ■

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