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SCIENCE WATCH:THE 1918 FLU EPIDEMIC
STALKING A KILLER

The CDC fights virus every year to prevent a disastrous pandemic
By M.A.J. McKenna STAFF WRITER

Two dozen policemen stand at attention on a deserted city street: upright, imposing, intimidatingly stern.

The camera has caught them in a desperate public emergency, yet it is hard to see uncertainty or fright in their bearing. From chin to cheekbone, they are muffled in surgical masks. Under the high police helmets, only their determined eyes are visible.

The newspaper photograph, yellowing and fragile, was taken during the worst natural disaster of the 20th century. It hangs in an office at the Centers for Disease Control and Prevention, next to a genetic diagram of the cause: the influenza virus, which killed 40 million people in the worldwide epidemic of 1918. The chief task of the scientists in the office is to ensure that the organism in one picture never again causes the panic and disruption of the other.

This month marks a key moment in that struggle. An international team of researchers is en route to the Arctic, to an isolated graveyard where the frozen bodies of flu victims might contain the only complete 1918 virus ever seen. A team in Washington is racing them to the same goal, re-assembling the virus from tiny genetic fragments recovered by cutting-edge research.

Meanwhile, the annual flu season is beginning. At this point 79 years ago, the victims of 1918 were dying.

Flu mutates unpredictably every year; once a generation, a virulent new variety sweeps the globe. The last major outbreak was 29 years ago. The next could come at any time.

“It is very, very likely we will see another pandemic,” said Dr. Keiji Fukuda, CDC’s chief of flu epidemiology. “It is impossible to predict how severe the next pandemic will be.”

We tend to take flu for granted: A menace that keeps us home for a few weeks with fever and headache, coughs and a dripping nose. But flu is much more serious than we recognize. In its mildest forms, its complications kill up to 20,000 Americans a year ---mostly the very old and very young, as well as those with heart and lung conditions or the impaired immune systems caused by cancer treatment or AIDS.

And in its lethal forms, it kills many more: 34,000 Americans in 1968, 70,000 in 1957 and at least 675,000 in the 1918 Spanish flu.

The Atlanta-based CDC helps to manage a worldwide detection system that tracks major and minor changes in flu each year. The data collected are analyzed at four major labs ---in Atlanta, London, Tokyo and Melbourne, Australia ---and then examined at a yearly late-winter meeting of the World Health Organization to predict which viruses will circulate in the next flu season.

The meeting dictates each year's vaccine, a juggling of the previous year's flu, the chances of change and the hard reality that it takes six months to produce enough vaccine to be useful. (CDC announced in April that the 1997 vaccine ---available now from public health authorities and doctors ---would protect against the Wuhan, Bayern and Beijing strains of flu.)

"You always face the possibility that you may not have had enough data at the time to make the best decision," said Helen Regnery, CDC's chief of flu strain surveillance. "But if you look at the last nine years or so, the matches between the vaccine and the currently circulating epidemic strain have been almost 100 percent."

The system has faults. It relies on predictions made almost a year in advance, and it depends on accurate, timely data gathered despite significant obstacles of crowding, poor communications and low funds.

"Infrastructure is really lacking in some countries such as India and Africa ---places with dense population and poor public health where new strains might emerge," Regnery said.

But the system worked well enough to catch a new flu strain in May, a virus that CDC initially feared might be the next killer variety.

Tests on samples from a Hong Kong toddler who died of viral pneumonia puzzled researchers there. Further emergency tests on samples airlifted to London, Rotterdam and Atlanta revealed that the flu the child had died from was a type that had never been seen in humans before.

Worse, it was a flu that usually infects only birds: The same type had killed millions of chickens in the United States in 1983, and 4,500 in Hong Kong last summer. Flu viruses live routinely in waterfowl, but don't infect humans until they have made an intermediate stop in another species, such as pigs.

CDC scientists were deeply unnerved. A new virus had emerged ---in China, the historic home of the most lethal flu strains. It had leaped species in an uncharacteristic manner. And it had appeared so late in the year that the vaccine-manufacturing cycle would have difficulty catching up.

"There was a chance that the pandemic had already started and this case was just the tip of the iceberg," said Fukuda, who was one of the CDC staff scrambled to Hong Kong to investigate.

The team found no evidence that the new strain had passed between people, a key requirement for a pandemic to start; for some reason, only the child was vulnerable. The first scientific paper on the case, written by a Memphis virologist who is one of the world's experts on flu, was published this week in the journal Nature.

CDC's flu branch spends much of its time on pandemic planning, designing international emergency efforts for when a deadly new bug does emerge. Their best estimate, Regnery said, is that even the most virulent virus could take months to circle the planet.

But "the advent of mass air travel certainly makes it possible that a pandemic could spread more quickly than it did in the past," Fukuda said. "The virus can span the globe in a matter of hours."

Scientists have done their best to build bulwarks against flu: the emergency plan, the extensive surveillance system, the recent addition of 10 CDC-funded labs in rural China. One challenge still puzzles them: public indifference. When a lethal virus reappears, our tendency to take flu lightly may be our greatest obstacle to stopping it.

"We're fascinated by Ebola, when the total number of people it kills is much smaller than the number of people who die each year from influenza," Fukuda said. "This virus comes around every year. It changes continually. It is a really difficult infection to control. And yet the popular perception is that it is no big deal."

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SCIENCEWATCH: THE 1918 FLU EPIDEMIC
`THE WHOLE WORLD WAS INFECTED'

On the anniversary of this lethally efficient flu, one scientist prepares to dig up a promising key to a mystery that killed millions
By M.A.J. McKenna STAFF WRITER

Seventy-nine years ago this Friday, the bodies of seven young men were lowered into the stone-hard ground of a snow-covered island so far above the Arctic Circle that polar bears have been seen in the streets of its only town.

The seven men were miners, who had come from the Norwegian mainland to dig coal in the icy Svalbard archipelago 720 miles below the North Pole. But instead of taking from the earth, they were added to it: Sick on arrival, they died within days and were buried in the wind-scoured cemetery of the town of Longyearbyen.

The spare white crosses above the graves are the miners' only monument ---and another kind of monument, too: They are the high-water mark of a wave of death that washed across the globe in the last year of World War I.

This week, an international team of researchers takes the first steps to end the seven miners' long isolation. Led by Kirsty Duncan, a charismatic young Canadian geographer, they will survey the grave site with ground-penetrating radar.

If they find what they hope to find ---that the bodies lie frozen in undisturbed permafrost ---they will return in a year to dig them up and sample their tissues. The samples will be analyzed at some of the most sophisticated infectious-disease laboratories around the world.

If conditions are perfect and the team is lucky, the secret the seven miners have kept for eight decades may be revealed:
The virus that killed 40 million people in the Spanish influenza epidemic of 1918.

40 million victims

There has never been an epidemic like the 1918 flu. The medieval Black Death killed as many people ---possibly 40 million Europeans, one out of every three ---but it took 150 years to do it.

The Spanish flu was more efficient. From March 1918 to the following February, it sickened and killed families, cities, regiments on the battlefield: 675,000 Americans, 90,000 people in the Philippines, possibly 20 million in India.

"The whole world was infected," said Dr. Jeffery Taubenberger, a U.S. pathologist advising the Canadian-led team.

In Atlanta, where 750 died, all public gatherings were banned. The San Francisco City Council required the entire population to wear surgical masks. Apocryphal stories from New York City said people got on subway cars and died before they reached the end of the line.

The toll was so great that it reduced average U.S. life expectancy by 13 years. It may even have changed history: The Treaty of Versailles that ended World War I but set the stage for World War II might not have been so punitive if peace-loving President Woodrow Wilson had not been disabled by flu during negotiations.

It was not what we think of now as flu ---the cough and sniffles, fever and muscle aches that send sufferers to bed for up to several weeks and lead, in the unlucky few, to potentially fatal pneumonia. The Spanish flu killed in days; its preferred victims were not the young and old, the usual targets of infectious diseases, but those in their 20s. And it killed horribly, triggering a massive immune reaction that saturated the lungs of its victims with blood and fluid, so they drowned from within. Contemporary accounts describe corpses as slate-blue from lack of oxygen and hemorrhage into the skin.

“There are stories of dying people whose appearance changed in two hours from white to black,” said Dr. Robert Webster, a flu expert and Memphis virologist advising the Canadian team. “There are stories of sick young soldiers being put in tents, and people outside watching (coughed-up) blood hit the tent walls.”

”Some aspects of the description
sound almost like hemorrhagic fevers, like Ebola and Lassa, that have come out of Africa,” said Dr. Charles Smith, a Toronto forensic pathologist on the team.

The Spanish flu killed more Americans than World War I, World War II, the Korean War and the Vietnam War combined, yet it is now barely remembered. Unlike AIDS, the other great plague of this century, it produced almost no art, no theater, no literature of grief. Only one slender novella, Katherine Anne Porter’s “Pale Horse, Pale Rider,” memorializes it. Yet it remains an urgent threat. The influenza virus mutates unpredictably every year; every few decades, it changes sharply enough to cause a worldwide pandemic. The last two, in 1957 and 1968, were mild in comparison to 1918 ---but no one can predict when such a deadly flu will come again.

The 1918 virus could tell us, if it could be analyzed. But there are only a few places on the globe where some trace of the killer may remain. The Longyearbyen cemetery is one of them.

On the trail of a killer

The Spanish flu has obsessed Kirsty Duncan for almost five years, a significant chunk of her life. The expedition leader, a Ph.D. who teaches climatology and geography at two Canadian universities, is just 30 years old.

Fine-boned and dramatic, with hip-length hair and the honed body of a former gymnast who still does 1,000 sit-ups a day, Duncan lives in a Toronto suburb with her husband, a British pediatrician. She works in her parents’ house several streets away, a comfortable split-level decorated with evidence of her avid enthusiasms: Gaelic textbooks, photos of her as a Highland sword dancer, and piles of overstuffed loose-leaf folders containing every letter and note she has written about the 1918 flu.

Her search started with a book: “America’s Forgotten Pandemic,” by Alfred W. Crosby, a little-known but detailed account of the flu.

“My interest was originally how climate change might affect disease,” she said. “I’d done work on plague and malaria and the connection between global warming and Lyme disease, and I was interested in the seasonality of flu. And then I read this book.

“I was amazed ---horrified. And I came home and said to my husband, `I will find out what caused this disease.’ “

That impulse launched her on a quest that earlier had defeated eminent scientists. For four years, she pored over death records from

Alaska, Iceland and Siberia, looking for a place where the unembalmed bodies of flu victims might be preserved.

Climate, political instability and the biology of the disease were against her. The flu virus reproduces and leaves the body within days of infection, and it is genetically fragile and breaks down quickly after death. She needed a site where victims had died quickly and been chilled immediately ---and where records existed to confirm those events.

Then a mountaineering friend from graduate school in Edinburgh told her several years ago about a hike he had led across a Norwegian glacier. They'd had terrible troubles, he said, with permafrost.

"I knew there had been flu in Norway," she said, her voice brightening with remembered excitement. "I knew from one of my professors that they had mined coal far north. And I guessed, if they were transferring people from the mainland to undertake mining, they might have brought the disease."

It was a good guess. After several years' work and many disappointments ---no church or government records from the era, no medical histories because the only hospital had been bombed in World War II ---she found coal company logs detailing the miners' deaths and burial in the company town of Longyearbyen.

Two more years of permission-seeking followed: from the Norse Polar Institute, the local government, the Norwegian government, the surviving relatives of the seven dead men. In May 1996, Duncan finally set out to meet the town.

She expected hostility but found extraordinary warmth, from the female governor of the territory, the schoolteacher who had translated the diaries, the minister who had championed her work to the local community. On the last day of her visit, at the minister's urging, she set out to visit the grave site.

"In my heart of hearts, I believe a cemetery is a sacred place, and what we propose to do is very hard for me," she said, her voice roughening to a whisper. "It is quite a distance from the church ---it's on a hillside, you can see it from anywhere in town ---and it was one of the longest, hardest walks of my life.

"It was white with snow, and the crosses were white. The ones I wanted were all the way at the back against the fence. I looked at them. I thought about how these young men were just starting out in life. And I asked their forgiveness for what I was about to do."

A team of medical detectives

Duncan has recruited a remarkable scientific team, volunteers attracted by the force of her personality, the challenge of a grueling expedition and the chance to solve one of the great medical mysteries of this century.

Included in the 11 are a geologist, a medical archaeologist, several pathologists and experts in virology and infectious disease from Canada, England and the United States. One of the leaders is Smith, a forensic pathologist who is officially an expert on suspicious deaths in children ---and unofficially an enthusiastic student of difficult exhumations.

This expedition, he acknowledged, is about as difficult as an exhumation can be. Sitting in his office in Toronto's Hospital for Sick Children, a crowded space containing a photo of a prized Hereford cow from his family farm and the cranial bones of an infant he exhumed in India as part of an Ontario murder case, he detailed a few of the problems.

"We are not absolutely sure yet that the crosses are where the graves are because the crosses were replaced for a royal visit in 1985," he said. "We don't know if the bodies were put into seven separate graves or one pit. We can't even be sure if they are in coffins. We don't know if they are frozen to the ground."

The team is moderately sure the bodies have been well-chilled since shortly after death. According to records, the corpses were placed in unheated storage at a time of year when the temperature was about 20 degrees, then buried deep enough to be below the line at which the ground remains frozen year-round.

But until they radar the site this month during their preliminary expedition ---in fact, until they begin to dig next year ---they won't know for sure.

"The first rule of exhumation," Smith said, "is that you never know what you're going to find until you look."

If the bodies seem accessible, the team will have to tackle the technical challenges of autopsying them in difficult conditions: short daylight hours, low Arctic temperatures and punishing wind.

The Norwegian government has ruled that the bodies may not leave the cemetery. The excavators may not be able to get the bodies out of the graves. And they will have to surround their site and themselves with elaborate safety precautions.

Though they believe the probability is slight, there is a chance the flu still might be infectious, and no one wants to be responsible for reviving the worst virus the world has ever known.

"If I can't be convinced that we can do this safely, I'm not going back," Smith said cheerfully. "But the chance of coming up with live virus is probably remote."

Many attempts, no successes

The Canadian exhibition is the most dramatic attempt to recapture the virus of 1918, but not the first or only one.

It has been an elusive quarry. Contemporaneous accounts make it clear that although Americans knew flu was communicable ---they held open-air

church services and stayed away from public places ---they had no idea how to combat it. Health authorities advised them to take laxatives and quinine salts and keep their windows open.

It wasn't until 1933 that a team of British bacteriologists, using a farm full of ferrets, identified the infectious agent as a virus. But the flu had mutated away from its deadly 1918 form; they could see only its shadow, by analyzing antibodies left in the blood of survivors. To this day, scientists have never seen the complete 1918 virus.

In 1951, a team from the University of Iowa exhumed and analyzed bodies from an Alaskan town where 80 of the 150 residents had died. But the bodies had not stayed frozen; no virus remained in the tissues. In the 1980s, Webster, a Memphis virologist and flu expert, unsuccessfully tried to isolate the virus from preserved autopsy specimens.

Ten years later, genetic research techniques are so improved that a second lab attempt has succeeded. Taubenberger, the American pathologist recruited by Duncan as an adviser, leads a team that has isolated 15 percent of the virus. It is a significant scientific achievement ---but it has not plumbed the medical mystery of what made the 1918 virus so lethal.

"It could be one genetic change that we haven't found yet," said Ann Reid, Taubenberger's chief collaborator. "It could be a combination of many genes, and possibly the relationship of the host to the virus. The biology is very, very complicated."

If the Canadian or American teams solve that puzzle, they still may have only contributed to history. Some flu scientists doubt the knowledge will be much use in the future. CDC's flu branch, for instance, initially was part of the Canadian expedition but has withdrawn.

But if the exhumations go well the agency may be forced to step back in; it houses not only the world's premier disease detectives, but one of only two labs in North America capable of handling an infectious organism as deadly as the recovered virus might be.

At the moment, though, they remain cool to the project. "In terms of preparing for the next pandemic, we already know what we have to do," said Dr. Keiji Fukuda, chief of epidemiology at the CDC's flu branch.

"For all practical purposes, it doesn't matter whether we're doing that in response to the 1918 virus or something completely different," Fukuda said.

So many uncertainties remain that members of the Canadian exhibition have disciplined themselves not to look too far ahead. Despite her passion for the search, Duncan in particular is sturdily pragmatic ---perhaps because, with the goal so close, hope feels like too great a risk.

"People ask me, am I excited, am I ready to go," she said not long before the team departed. She had been up very late the night before. She pulled her long hair off her neck with a weary gesture and ran a finger along the edge of a milk crate stuffed with her notes.

"It has been such a long process; there have been so many hurdles, I don't allow myself to get excited anymore. But I imagine myself back in that cemetery. I promised them I would find out what killed them, and I will."

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SCIENCE WATCH: THE 1918 FLU EPIDEMIC
U.S. team delivers first look at 'Spanish flu'
By M.A.J. McKenna STAFF WRITER

To search for the cause of the 1918 flu, Canadian researcher Kirsty Duncan is leading a team of scientists almost to the ends of the Earth. A second American effort to recover the killer virus is taking a different route, to the limits of a particularly challenging form of laboratory science.

The second effort may reach the goal first.

Working from a tiny piece of preserved tissue uncovered in a crammed storage facility, the U.S. researchers have gotten the first glimpse of the virus that killed 675,000 Americans ---including the 21-year-old Army private from whose lungs the sample came.

"By the time we get back with specimens, (the Americans) may have the whole genome characterized," said Dr. Charles Smith, a member of the Canadian team.

The American group, molecular pathologists and biologists at the Armed Forces Institute of Pathology in Washington, didn't set out to find the flu virus. Their goal was to advertise their lab's unique abilities at unwinding genetic codes from decades-old anatomical samples. The institute has 3 million autopsy specimens, preserved in wax or liquid or on glass slides, that date back almost to the Civil War.

"We asked ourselves what we could do to highlight the utility of our techniques and the riches of a collection that goes back 100 years, and what came out of that discussion was the 1918 flu," said Dr. Jeffery Taubenberger, who led the work with biologist Ann Reid. "It was a medical mystery; no one knows why that virus was able to sustain such an epidemic. But the AFIP archives had about 100 cases in it, and that was how we got started."

They had set themselves a daunting task. No one knew whether the fragile genetic material of flu could survive in tissue that had been fixed ---soaked in formaldehyde and embedded in paraffin wax ---for so long. They weren't sure it was there at all. Though flu victims can be sick for weeks before dying, that is usually due to subsequent infections; the influenza virus leaves the body within six days.

The unique qualities of the 1918 virus bent the odds in the researchers' favor. It killed its victims within several days, sometimes within hours.

"Their lungs filled up with blood and fluid ---they literally drowned," Taubenberger said.

So the virus might have been trapped in their tissues when they died ---and if the team could find samples from those victims, their chances of finding the virus increased. They screened lung tissue from 28 cases chosen at random, found seven that merited a closer look, and checked them microscopically.

Only one showed the characteristic inflammation and cell damage caused by the flu virus rather than bacteria; in the first round of testing, only that sample still contained the genetic material of flu. The team had caught a glimpse of the footsteps of the killer.

Using a technique known as polymerase chain reaction, which makes repeated exact reproductions of genetic material, Reid and Taubenberger copied out the gene fragments they found. After two years of work, they were able to isolate five pieces of the two key genes for proteins that distinguish flu viruses from one another: hemagglutinin (H) and neuraminidase (N).

When they published their research last March in the journal Science, the team had identified 7 percent of the genes that make up the 1918 virus. Now they have achieved 15 percent.

Analysis of the gene sequences proved ---and disproved ---several useful points. It confirmed a long-held suspicion that the 1918 virus was of a type called H1N1, which disappeared from circulation in 1957 and reappeared in a milder form in 1977. It showed that the 1918 flu wasn't, as had been thought, a virus that passed directly from birds to humans ---potentially making it harder for human immune systems to handle ---but had emerged in the classic manner, making an intermediate stop in pigs.

The work also debunked a theory that the virus was so vicious because it possessed a unique genetic structure that allowed it to penetrate cells more easily. What the analysis couldn't achieve was any proof of what made the 1918 virus so lethal.

Taubenberger and Reid are continuing their work, but they may never reach that goal.

"It is possible we could generate the whole sequence of the 1918 virus, have it on paper in front of us, and still not be able to point to anything and say, `This is the reason why this one was so bad,' " he said.

One thing that may help is finding a second case to analyze. There are cases in the archives that the team hasn't examined, and if the Canadian expedition is successful, there may be virus remnants in the Norway corpses.

But the archival cases and the Canadian deaths occurred in late 1918. What the Washington team wants most, and hasn't yet found, is a case from earlier that year.

"There was a huge spring wave of influenza in 1918, and hundreds of thousands of people got sick, but the death rate was much closer to a normal epidemic," said Reid, Taubenberger's collaborator. "Then in August it broke out again, this time with a very high death rate. We theorize there was a genetic mutation between spring and fall that caused it to be much more lethal."

That may be difficult to prove. There was little alarm over the spring wave of flu because relatively few people died.

When they did, it was in the classic lengthy manner. If they were autopsied, it was long after the flu virus had left their bodies. While the team searches ---so far without success ---it is working on a technique to preserve the genetic material it has found.

That way the genes can still be studied when the tiny sample is used up, and the 1918 flu will not be lost again.

"Ultimately, one of the most important things we could do is to find a case in some archive somewhere in the world" from before the fall epidemic, Taubenberger said. "I would feel more comfortable having more cases to work with. But I think it is possible that this is the only positive case there is."

Chart: THE FLU OF 1918

-March 1918: As war rages in Europe, an epidemic of flu breaks out in towns, factories and Army camps across the United States. Most victims recover. Within a month, members of the British Expeditionary Force in France are knocked out by flu and the virus begins to affect front-line German troops.

-May-June: The epidemic diminishes in the United States but crosses to Britain and Spain, where it is given the name "Spanish flu."

- July-August: Flu cases diminish among armies in France and Britain but emerge in Switzerland, Denmark, Norway, India, China, New Zealand, the Philippines and Hawaii, and among troops in the Panama Canal Zone.

-Aug. 22: A deadly variety of flu breaks out in Brest, France, an offloading port for U.S. troops. A week later, flu cases spread to Boston.

- Sept. 13: The U.S. Public Health Service releases the first bulletin on the flu. By month's end, 2,200 U.S. soldiers and sailors are dead of flu.

- Sept. 24: - Oct. 10-11: 759 people die in one day in Philadelphia; military personnel are barred from entering Detroit to prevent infection.

-Nov. 18: Three U.S. treaty negotiators get flu at Paris peace talks; two weeks later, the lead U.S. negotiator dies of flu.

-March 1919: Spanish flu wanes worldwide.

: (Source: America's Forgotten Pandemic; Alfred W. Crosby; Cambridge University Press, 1989.)

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SCIENCEWATCH: THE 1918 FLU EPIDEMIC
THE SMART VIRUS
Small mutations allow the flu to reinvent itself every year
By M.A.J. McKenna STAFF WRITER

The Canadian and U.S. teams in pursuit of the 1918 influenza virus have a wily adversary.

Flu has been extensively studied ---almost 34,000 scientific papers have been published on it ---but never beaten. Every year, there is risk of a deadly world-traversing virus emerging ---and unlike some other deadly infectious diseases, there is no lifetime vaccine.

"Flu is a smart virus," said Helen Regnery, who tracks genetic differences in the virus for the Centers for Disease Control and Prevention in Atlanta. "It has figured out how to change its nature and its genome to keep surviving. It likes to keep us on our toes."

Non-scientists often use "flu" as a synonym for "cold," but few flu sufferers have mistaken one for the other. Flu causes not just fever, sore throat and congestion, but headache, muscle aches and fatigue, which develop so abruptly that victims often can tell exactly when they were infected.

The virus enters cells that line the breathing passages of the lungs, turns them into small factories for reproducing many more copies of the virus, then leaves the body within six days of infection in droplets expelled by breathing or coughing.

Although flu can keep victims in bed for weeks, and kills up to 20,000 people a year in the United States, that is usually due to secondary bacterial infections such as pneumonia. Since 1918, rapid deaths from primary flu have been considered uncommon.

Flu has an uncomplicated structure: a coil of genetic material enclosed in a protein coat. But the genetic material is not DNA, the sturdy, double-stranded spiral staircase of nucleic acids, familiar from high school biology textbooks, that serve as blueprints for living things by directing cells to make proteins. Instead, it is RNA, a single-strand version that is more fragile and more vulnerable to errors when reproducing. That high error rate accounts for the many small mutations, called "drift," that change flu strains slightly from year to year; some

of the mutations change the proteins on the virus' surface, so the immune system no longer recognizes them.

Flu also changes in more substantial ways, called "shift." Shift is most likely to produce the viruses that cause pandemics, because it makes variations of flu so different from previous ones that people have little or no defense against them. It happens like this:

Although we think of flu as a human disease, it lives routinely in waterfowl and can infect species from seals to horses to whales.

Most species can be infected only by certain varieties. Humans, for instance, don't catch horse flu. But some species are vulnerable to several varieties. Pigs, for instance, have cellular receptors that allow them to be infected by both bird flu and human flu.

Flu's genetic material has weak links, allowing the RNA to break easily into eight segments. That fragility is one reason the virus has been hard to recover in long-preserved samples, but in a living cell, it works to flu's evolutionary advantage.

In a pig, for instance, the fragments of a mild human flu and a bird flu completely foreign to the human immune system can combine to form a new virus. Just that process ---avian flu, human flu and the pig as the mixing vessel ---produced every severe flu this century, including the lethal virus of 1918.

To cause one of the worldwide epidemics called pandemics, a flu virus must be not only new to the immune system, but easily transmitted between humans and capable of causing severe illness.

Clever though it is, flu doesn't always clear all three hurdles. The new flu in one child in Hong Kong last summer did not infect other humans, and the swine flu of 1976 did not cause serious disease.

But every so often, flu's random evolution wins the trifecta. Records of pandemics go back to 1510, and there were at least four in the 1800s. There have been three global epidemics this century: 1968, when 34,000 Americans died; 1957, when 70,000 died; and 1918, which killed 675,000 Americans and 40 million people around the world.