The next pandemic virus may be circulating on U.S. pig farms, but health officials are struggling to see past the front gate

By Helen Branswell
The 2009 influenza pandemic appeared to come out of nowhere. It started as what seemed like a lethal outbreak in Mexico, then spread north of the border. By the time health officials learned that the virus responsible for the alarming explosion of cases was new and an infection threat to most of humankind, they had no way to keep it from spreading around the world. By a stroke of luck, symptoms were mild in the vast majority of cases. What if next time we are not so lucky?

That question weighs heavily on the minds of influenza scientists and public health planners as they prepare for the next big outbreak. And there will be a next time. Flu viruses mutate constantly. Occasionally those changes result in viruses so different from what our immune systems have seen before that they are able to trigger global waves of disease, or pandemics. Someday there may be a vaccine that can fend off all subtypes of influenza, but such a vaccine remains a dream for now. So new viruses can and will come at us from birds or pigs or other animals. The best we can do is try to spot new invaders soon enough to get a jump on producing vaccines against those particular bugs, to shorten the time from first infections to mass immunizations. No one wants a repeat of 2009, when a vaccine arrived about the time the outbreak was peaking and public interest was waning.

But spotting new threats can happen only if scientists know what viruses are circulating among the species most likely to give rise to new pandemic viruses—birds and pigs. And whereas surveillance in the former has improved over the past five or six years thanks to concerns about bird flu (the H5N1 virus), scientists know too little about the viruses that infect the estimated 941 million domesticated pigs around the world.

Intensive monitoring of pig viruses is unlikely to come any time soon, however. Most pork-producing countries do not test their pigs at all, and in some that do—such as the U.S.—the testing is done on behalf of the pork producers, who have little economic incentive to share what they find. The reason: pig farmers know pork prices plummet when pigs and flu are linked in the news. In the U.S., government agencies have pieced together a new program they hope will extract badly needed data without threatening the livelihood of producers. But many human health experts fear the compromises made to get pig farmers onboard may hobble the effort.

**INCREASING MUTATION RATES**

You could call pigs the Achilles’ heel of global influenza surveillance. For the animals and the people who raise them, flu is more of a nuisance than a serious threat; it typically causes only mild symptoms in pigs. Swine influenza is not even a reportable disease, a classification saved for diseases deemed a threat to the entire industry, such as foot-and-mouth disease. On the other hand, pig flu viruses can be a big problem for the general population. That is because pigs are a genetic crucible for new flu viruses. They can be infected with flu viruses from birds, other pigs and people, creating opportunities for a melding of genes in new combinations known as reassortants. The fear is these new hybrids will prove capable of infecting people readily, while being sufficiently foreign to cause serious illness once they do.

Since the start of the 2009 pandemic, scientists have tried to piece together how the responsible virus emerged and where. Although the puzzle is still missing many pieces, what they have been able to surmise only underscores the need for vigilance.

For decades the flu viruses that infected pigs remained largely stable. They were genetic descendants of the influenza A virus that caused the 1918 Spanish flu pandemic, an outbreak that killed upward of 50 million people. This family of viruses is named H1N1; the H stands for hemagglutinin and the N for neuraminidase, two proteins on the pathogen’s surface that laboratories—and immune systems—use to tell one flu virus from another. (There are 16 groups of H proteins and nine groups of N.)

**Emerging threat:** While the flu pandemic of 2009 was apparently mild, there is no way of knowing whether the next one will be a重复 or more closely resemble the killer disease of 1918.

**Early warning:** After the 1997 avian flu scare, researchers developed pretty good surveillance programs to detect potentially deadly viruses that might jump from birds to people.

**Blindsided:** The 2009 pandemic underscored the possibility that the greatest threat may come from pigs, not birds, because it is typically easier for pig viruses to make the jump to people.

**Hamstrung:** Economic considerations make it harder to get viral samples from pig farms in a timely manner, which frustrates health officials who want to be better prepared for the next pandemic.
proteins.) Distant cousins have also been infecting people for most of the decades since the 1918 pandemic. The pig variants, known as classical swine flu viruses, evolved far more slowly than the human varieties. This picture changed dramatically about a dozen years ago. For unknown reasons, influenza viruses in pigs began to evolve at a dizzying rate in North America, where enormous numbers of pigs are raised.

The U.S., in fact, is the world’s second-largest pork producer, after China; 115 million hogs went through U.S. slaughterhouses in 2009. Commercial pig farms vary in size and style of operation. These days many operations segregate the animals by phase of development, keeping pregnant sows away from piglets, for example, to cut down the spread of profit-threatening diseases.

In 1998 herds in Minnesota, Iowa and Texas were found to be infected with a new H3N2 virus, a so-called triple reassortant containing classical swine flu virus genes, along with genes from viruses that normally infect birds as well as those that infect people. Since then, other triple reassortant viruses have formed and spread. These included yet another version of H1N1, as well as an H1N2 and an H3N1 virus. Even H2N3 viruses were briefly spotted in pigs in Missouri in 2006, a potentially dangerous turn of events given that no one born after 1968 has any antibodies to the H2 family of viruses. H2 viruses are high on the list when scientists muse about which ones might go on to cause a future pandemic.

Researchers at the U.S. Department of Agriculture and at diagnostic laboratories reported on the new viruses in scientific journals. But most scientists and officials who focus on the human health side of influenza were distracted by a different and dangerous threat: bird flu. In 1997 an H5N1 virus surfaced in Southeast Asia, traditionally thought of as the epicenter of new

Illustration by Emily Cooper

Replication and Reassortment

Influenza viruses are well adapted to rapid evolution. First, however, they must infect a cell because they cannot replicate on their own. The diagram below shows how and when flu viruses get into human cells and under what circumstances different strains can mix and match genes with one another, yielding potentially dangerous new types.

No Infection

Viruses that infect birds do not normally also infect people. The hemagglutinin protein on the outside of the virus has trouble hooking up to the receptor of the human cell.

Infection and Replication

For a flu virus to easily infect people, its hemagglutinin (H) protein has to latch on to the receptors on the host cells of the respiratory tract. The cell absorbs the full complement of eight viral genes, which in turn direct the cell’s machinery to make more viral particles.

Gene Mixing

When a single cell is infected by two different strains of flu, copies of the viral genes from both strains can get mixed up and are sorted by the cell into new viral particles without regard to their original makeup. Only one of several different possible reassorted strains is shown.

RNA

Hemagglutinin (H)

Neuraminidase (N)

RNA

Avian influenza

H

N

Human host cell

Nucleus

Host cell copies viral RNA

Human influenza virus

Host cell copies viral RNA

Strain 1

Strain 2

Strain 3 (reassorted virus)
Making a Pandemic Flu

The pandemic flu virus of 2009 belongs to a group called H1N1 viruses. Immunity to one H1N1 virus does not automatically protect you against the others. Part of what made the 2009 H1N1 virus so alarming is that its recent forebears infected three species—humans, birds and pigs. In other words, the virus contained genetic material that was unfamiliar enough to the human immune system to cause a pandemic, albeit a mild one. We may not be so lucky next time.

Complex Virology

TESTING PIGS

The irony of that juxtaposition is not lost on the influenza scientists, who remember how aggressively the U.S. pushed China, Indonesia and other Asian countries to be more transparent about their H5N1 outbreaks. Guan and others are frustrated by the dearth of surveillance data on pigs, not just from the U.S. but elsewhere as well. Surveillance data from the U.S. are inadequate, but there is virtually no monitoring for swine influenza in South and Central America, Africa, India and some other parts of Asia. “The current situation is really not at all comforting,” Peiris declares. “We know the pathway,” says Guan of the role pigs can play in the creation of novel flu viruses. “Why are we not looking?”

In the U.S., a better question might be “Why aren’t they sharing?” Farmers have historically had their pigs tested for flu, often at the diagnostic laboratories of the National Animal Health Laboratory Network (NAHLN). And companies that make flu vaccine for hogs need to know what flu threats the animals face so that they can tailor their vaccines accordingly. But the information that is gathered by the animal health sector is rarely shared with the researchers and officials who safeguard human health. In fact, in the wake of the 2009 outbreak, testing for flu on pig farms screeched to a halt. “Basically the producers really didn’t want to know, and so the usual stream of respiratory specimens going into the NAHLN labs dried up,” says Nancy J. Cox, head of the influenza division at the Centers for Disease Control and Prevention.

The priorities of these labs and companies are shaped by what is best for pigs and their owners. The NAHLN labs—often housed in universities, such as the University of Minnesota and the Iowa State University—work for the farmers, their clients. Any findings, positive or not, are kept confidential, explains Montse Torremorell, who holds a chair in swine health and productivity at the University of Minnesota. “There is a lot of actual sequencing surveillance, if you will, but that information is fed back to the people who have submitted the samples.”

Noteworthy findings, such as the discovery of the first triple reassortant, H3N2, do eventually end up in the scientific literature, but the process can take a year or longer. That is hardly a stand-in for real-time surveillance, which would give human health officials a current picture rather than a historical perspective. Every so often, someone catches swine flu directly from a pig, and the CDC gets a call. (For example, it happened twice this fall. Fortu-
nately, both cases turned out to be isolated episodes.) But such calls generally come too late to allow for a thorough investigation. The pigs “had often gone off to slaughter by the time we were able to figure out what the exposure actually was,” Cox says.

Efforts by other researchers to shed light on the kinds of viruses circulating in pigs have also met with resistance. Richard J. Webby, head of the World Health Organization’s collaborating center for influenza at St. Jude Children’s Research Hospital in Memphis, encountered the problem when he and a few colleagues tried to set up a short-term study to swab seemingly healthy pigs for flu viruses. In a bid to gain access to the animals, Webby’s team promised to put all the specimens it collected into a freezer for three months before studying them. This was a good faith gesture designed to assure farmers who cooperated that they would not find public health folks in hazmat suits at their farm gate a week after the swabbing took place. Webby says the offer, which was accepted by several farmers, was made to “guarantee the wheels.” Some producers probably would not have signed on without it, he acknowledges.

At present, though, far too few genetic sequences of viruses found in pigs are being uploaded to online databases such as GenBank or GISAID, where they could be viewed by flu researchers anywhere. That has left the human health researchers with a giant blind spot. “You couldn’t possibly say that the sequences in GenBank or GISAID or anywhere else are representative of what is actually circulating in pigs at the moment,” Cox says. “And this is what the public health side is very concerned about. We understand all of the issues on the agricultural side. But we want to work toward a solution where there is a greater sharing of information that is available.”

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COOPERATION NEEDED

The CDC started down the road of greater cooperation even before the 2009 pandemic, negotiating with the USDA on a program that would see the findings of animal health diagnostic testing shared with the human health side. But the program, which is still getting off the ground, cannot work without the cooperation of pork producers, who have to date been reluctant to support what many see as a bid by government to meddle in their affairs. “The pigs are owned by the farmer. And what happens to their pigs is the farmer’s business, not the government’s business, as long as the infection that is going on in those pigs is not what’s termed a program disease that is considered to be a risk to the national herd,” says Paul Sundberg, vice president for science and technology for the National Pork Board.

To overcome the farmers’ hesitancy, the CDC-USDA surveillance system has several key compromises built into it. For starters, anonymity is assured. Viruses found in specimens that producers submit to diagnostic labs may be fed into a more widely accessible surveillance system. Yet unless a producer gives prior consent, anything that might identify his or her farm is stripped from the data before they are passed on. The human health officials can tell which state the virus was found in but not which particular county or farm. “The anonymous surveillance stream is the default, meaning that test results from the surveillance will be provided to the program anonymously. No owner or submitting veterinarian information will accompany the data,” says John R. Clifford, the USDA’s chief veterinary officer.

Producers can agree to let identifying information remain attached to the data, but few are expected to drop the shield of anonymity. The system’s rules also stipulate that if a person is infected with a swine influenza virus, the owner of any herd that person had contact with must give consent before authorities can test the pigs. If the CDC sees a human case or a virus that looks like it might be able to make the jump to people, would the anonymity veil be lifted in the interest of protecting human health? That is not yet clear. Sundberg says if the CDC saw a problematic virus, it could alert the relevant state health department to be on the lookout for human cases.

Producers are not uncaring about the threat swine flu viruses hold for people, says Sundberg, who supports the new CDC-USDA surveillance system, but they think the threat is sometimes exaggerated. Millions of pigs come in contact with people every day, yet human cases of infection from pigs are rare. Farmers saw what happened to Arnold Van Ginkel, the Canadian producer whose herd was the first in the world to test positive for pandemic H1N1. Van Ginkel’s pigs recovered, but he had to put down the animals because no one would buy them.

Although the number of viral samples submitted to the new CDC-USDA surveillance system started increasing in the second half of 2010, many doctors and epidemiologists fear that the built-in compromises are still too restrictive. They worry that they will not be able to identify new pig viruses or to detect the jump from a pig to a person in time to make a difference to human health. They have not given up on getting better data. The CDC’s Cox and Ilaria Capua, who heads a World Organization for Animal Health reference laboratory in Padua, Italy, are organizing a meeting in Italy in early February of key human and animal health agencies and scientists to try to find a way to overcome the barriers. Capua is cautiously optimistic that there are ways around the obstacles. “We just have to figure them out,” she says.

The politics of pork may be sluggish, but influenza is evolving at an alarming rate. “The biological rules have changed in the last 20 years, and so I think the thinking has to change,” says Earl Brown, a virologist who specializes in influenza evolution at the University of Ottawa. Pork producers stand to lose a great deal from any negative publicity. If a virulent successor to the 2009 pandemic virus emerges from pigs, however, everyone loses.