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OF SWINE AND MEN

Scientists study H1N1's past to predict what the virus has in store

By [Laura Sanders](#)

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As viruses go, H1N1 is a genetic pip-squeak. Like its influenza brethren, it possesses only eight genes. Yet those few genes are telling researchers a complex story about where this newly infamous virus came from, and, more importantly, where it might go.

That story began about a decade ago, when an infectious virus was busily packing pieces of its genetic material together, preparing to burst out of a throat cell and infect other cells in its host pig.

This virus was already the result of a genetic shuffle involving a human influenza, an avian influenza and a swine influenza, genetic sleuthing reveals. At the same time, a different virus — itself a mixture of a swine influenza and an avian influenza — was packaging its genetic material in the same cell in the pig's throat.

In an exodus-induced kerfuffle, a wayward piece of viral genome was mistakenly put into the wrong package, creating a virus never before seen. Sometime in the past decade, researchers estimate, the pig harboring this new mix-and-match virus passed it to a human, who launched its spread to thousands of people around the globe.

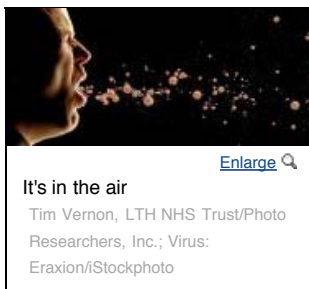
"The confusion at the beginning was that some of the virus's segments were coming from birds, some were coming from pigs, some were human," says molecular epidemiologist Hossein Khiabani of Columbia University. "What is this? This is a monster."

This dizzying tale of genetic mingling ultimately resulted in the H1N1 influenza strain currently circling the planet. This virus takes its name from its particular versions of two proteins, hemagglutinin and neuraminidase. Although this combination of H and N has appeared before in seasonal influenzas and most memorably in the pandemic flu of 1918, the virus circulating now has qualities that make it distinct enough to demand attention.

Such a history might suggest that today's H1N1 — declared by the World Health Organization on June 11, 2009, to have caused a pandemic — is ready to go hog wild, morphing into new forms that can easily thwart human immune systems and foil drugs. But new evidence, furiously collected during the virus's year or so on the world stage, hints at a different picture. Instead of a deranged homicidal killer on the rampage, this virus appears to be a more restrained villain.

"It seems that the intrinsic ability of this virus to cause disease is not that different from seasonal viruses," says Ruben Donis, who heads the Centers for Disease Control and Prevention's molecular virology and vaccines branch, based in Atlanta. But these are early days, he cautions. "This is all based on very preliminary numbers that are subject to change."

Emerging data from human infections and laboratory experiments on this swine-origin H1N1 suggest that the virus spreads no faster than the seasonal influenzas that circulate every winter. And studies hint that the human immune system has underappreciated advantages in combating the infection. Other research has found that the virus's genome isn't



It's in the air

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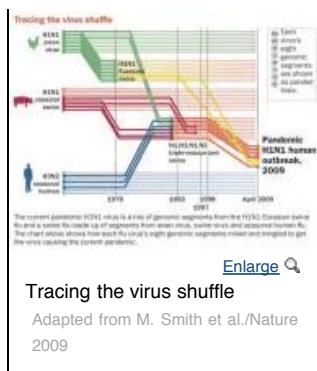
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changing at an alarming rate or in important ways. Like accents, the virus has taken on certain regional twangs, but none seem to be particularly menacing. Another study in animals finds that the virus didn't jump at the chance to mingle its genetic material with other strains of influenzas, even when the viruses

infected the same cells at the same time.

While the virus's genome is missing some of the worst danger signs of past pandemics, it has picked up a few new tricks that might be cause for concern. And just because the virus hasn't yet morphed in a dangerous way doesn't mean it won't. Now that the virus has a huge new playground in the human population, the possibility of its recombining with other influenzas can't be dismissed.

"Once we think we have this virus figured out, the virus shows us otherwise," says influenza expert Daniel Perez of the University of Maryland in College Park.

Predicting exactly what will happen is impossible. The virus may grow up to replace the seasonal flu viruses, or it may grow up to become an additional burden to contend with each winter. It may morph into a dangerous killer. Or it may not change much at all, existing only as a memory of the swine flu scare of '09 and '10.

Around the globe

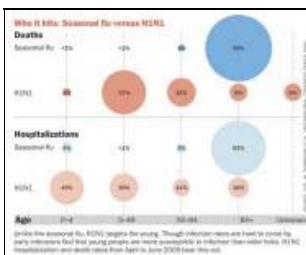
One of the reasons public health officials are keeping such a close eye on this H1N1 strain is that some important parts of its makeup are unrecognizable to most people's immune systems — presumably setting the stage for it to go ripping and snorting through the global population. But data from animal models and patient reports suggest that this influenza's movements, propelled by sneezes, coughs and germ doorknobs (see "The skinny on the bacon," Page 26), look more like those of seasonal influenzas than disastrous pandemics of the past.

If the devastating 1918 pandemic flu was an Olympic sprinter, dashing to the finish line in just seconds, this pandemic strain is "the guy running in Central Park," says microbiologist Peter Palese of Mount Sinai Medical Center in New York City.

The ways the virus is transmitted, how easily it spreads through contact and how long before symptoms show up are the same as what experts estimate for seasonal and other pandemic flus, says epidemiologist Justin Lessler of Johns Hopkins University in Baltimore, who co-authored a report that appeared in the Dec. 31 *New England Journal of Medicine*. "I don't think there's any evidence that this virus is any different," he says.

Lessler and his colleagues examined an H1N1 outbreak in a New York City high school. From that data, they estimate that the virus moves through the population slightly less efficiently than some previous seasonal influenzas. About 14 percent of people who came in contact with an infected person ended up with influenza symptoms. An infectee develops symptoms in about 1.4 days, a length of time similar to that of other influenzas, the team also reports. And 2.7 days elapse between when an infector feels sick and the newly infected feels sick, too.

Another study published in the same issue of the *New England Journal* examined household transmission rates and found that the pandemic virus is less likely to move from one person to another than some of the viruses



Who it hits: seasonal flu vs. H1N1

Source: CDC, W. Thompson et al./International Congress Series 2004

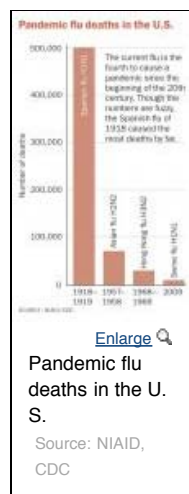
responsible for past pandemics. Simon Cauchemez of Imperial College London and colleagues found that, on average, about 10 percent of people living with a person infected with H1N1 come down with the flu. For seasonal flus, the same measure is anywhere from 10 to 40 percent.

A study in guinea pigs shows similar results. The virus replicates and transmits in the animals at rates close to those of a seasonal influenza strain, Palese and colleagues report in the January *Journal of Virology*.

The key to avoiding infection despite exposure lies with virus-destroying antibodies. These tiny patrollers roam the body on the lookout for harmful particles. When a threat is detected, the antibodies hitch on to the invader and call in other immune system attack dogs to prevent the virus from taking hold.

An inability of antibodies to recognize H1N1's proteins may explain one of the most ominous pieces of news about this virus: It seems to target young people. The CDC estimates that from April through December 12, 2009, about 50 million people under the age of 65 became infected, compared with about 5 million people over age 65.

In contrast, seasonal flu typically infects older people. More than 90 percent of deaths from seasonal influenzas occur in people 65 and older, the CDC reports. With the current H1N1 influenza, researchers estimate that people younger than 65 account for more than 80 percent of total deaths.



People born in the earlier part of the 1900s may be protected because their immune systems have seen influenzas similar to the current H1N1 and have developed antibodies against them, while the immune systems of young people have not.

"The prevailing theory — there is not very strong evidence yet, but there is some evidence — indicates that these folks have greater immunity than younger folks," Donis says. The thinking is that exposure to many viruses primes those immune systems to attack quickly, while young people's naive immune systems are caught flat-footed, lacking antibodies to attack this pandemic H1N1.

More studies are needed to fully understand how immune systems defeat influenzas. "Immunity is complicated," Donis says. "How all these mechanisms play out in the guy that is shedding virus, or the person that is shaking hands or breathing in droplets after someone sneezes or coughs, is still a very complicated biological process that we don't understand completely."

Younger folks are more susceptible than older people to getting the new H1N1 virus, but its overall threat to a young person is still proportionally similar to that of any seasonal flu, Palese says.

The number of deaths from pandemic H1N1 are estimated to be much lower than that of seasonal flus: On average, about 36,000 Americans die from flu-related causes each year, according to the CDC, while the current pandemic is responsible for an estimated 11,000 deaths from April through December.

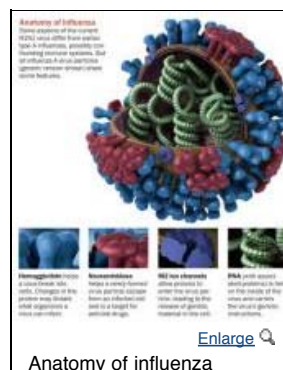
"It's the same rate," Palese says. "That has been really overlooked. It is not more virulent per 18-year-old, or per 25-year-old, than the seasonal one."

The inside counts

Another study finds that the virus isn't as unrecognizable as its outer proteins had led scientists to believe. A hidden familiarity might help people fight the virus once they've been infected.

Antibodies latch on to proteins on the outside of virus particles but are unable to detect what's on the inside of the virus. A different faction of the human immune system is formed by cells that recognize foreign proteins on the outside *and* on the inside of viruses. These cells, a type of T cell, are an underappreciated arm of the immune system and might be doing some of the immune system's heavy lifting, says Bjoern Peters of the La Jolla Institute for Allergy & Immunology in California.

In a study published December 1 in *Proceedings of the National Academy of*



Sciences, Peters and his colleagues addressed how familiar the virus is to the immune system. “We were essentially asking, how is this virus different, from the immune system’s point of view?” Peters says.

Dan Higgins, provided by CDC,
Douglas Jordan

As expected, proteins such as hemagglutinin and neuraminidase that decorate the outside of the H1N1 virus differed from proteins in earlier seasonal viruses, and as a result, were unfamiliar to most people’s antibodies. But proteins on the inside of the virus were quite similar to past influenzas, Peters and colleagues found. Because of this similarity, T cells might be able to quickly begin neutralizing cells once they are infected. “While there’s no immunity against the surface, there’s plenty of immunity against the internal proteins,” Peters says. The same study found that blood samples taken in 2007 from the general U.S. population had some immunity against the pandemic strain, thanks to T cell immunity.

“We believe we have a reason why the incidence of severe disease isn’t that high, based on the fact that people have T cell immunity,” Peters says. “You would expect that this is going to be a very severe, deadly pandemic if you have no immunity. Obviously, as we know, that’s not how it turned out.” A strong T cell reaction probably reduces the severity of influenza infections, clearing virus-laden cells before symptoms get bad.

Not out of the woods

Influenzas are notorious for playing fast and loose with their genomes — mutations are introduced as the virus replicates and gene segments are swapped with other viruses in a process called reassortment. Reassortment is responsible for the repackaging errors that, in part, created the H1N1 pandemic influenza. This genetic recklessness confounds immune systems and worries public health officials.

Early results from animal studies suggest that pandemic H1N1 isn’t eager to reshuffle its genetic deck, even when the influenza is infecting the same cell as another virus at the same time — a prime opportunity for gene segments to get combined in new ways. Perez and his colleagues infected ferrets with seasonal influenzas and the H1N1 strain and found no signs of new viruses, the team reported online August 25, 2009, in the non-peer-reviewed journal *PLoS Currents: Influenza*.

The results don’t mean that those viruses aren’t exchanging genes, Perez says, as low levels of reassortment could go undetected. Perez and his colleagues are currently testing more and different versions of the virus for their propensity to mix. Scientists don’t yet understand why only some viruses reassort and under what conditions they do so.

So far, sequences of virus from infected people don’t show signs of reassortment, either, Perez says. “Epidemiological data suggests that there are not reassortments happening, at least not this season,” he says. “That doesn’t mean that next season, things might not change a little bit. It’s a question that’s always an open question. We don’t have an answer for that.”

Researchers have, however, already pinpointed genetic changes, mutations acquired during the virus’s replication, that enhance its ability to make copies of itself in human cells.

Bird influenzas typically have the amino acid glutamate at a particular spot in a specific protein. This glutamate, says virologist Andrew Mehle of the University of California, Berkeley, dampens avian viruses by keeping them from replicating well in human and swine cells. To researchers’ surprise, H1N1 — which obviously has no problem prodigiously replicating in humans — carries this birdlike glutamate. But Mehle and colleague Jennifer Doudna, also of UC Berkeley, might be able to explain this.

The researchers found two different mutations that are able to overcome the hindering glutamate, allowing the pandemic virus to reproduce easily in humans. These mutations represent “a new and unusual strategy compared to what usually happens,” Mehle says. Avian influenzas with these changes were able to replicate better in human and swine cells, Mehle and Doudna report December 15 in *Proceedings of the National Academy of Sciences*.

Molecular epidemiologist Martha Nelson of the National Institutes of Health in Bethesda, Md., and her colleagues compared the genetic sequences of H1N1 from around the world to see if the virus had taken on other genetic changes as it copied itself. The team’s analysis, published online November 5 in *PLoS Currents: Influenza*, finds that the virus shows slight regional differences. On the basis of these differences, Nelson and colleagues divided it into seven distinct clades. None of the differences among clades seem to be ominous,

though, Nelson says. “In the grand scheme of things, these clades are still very closely related,” she says.

Likewise, scientists at the World Health Organization report that all of the sequenced H1N1 clades are very similar to the original strain, rendering the H1N1 vaccine — designed to combat the original sequence of the virus — accurate and effective.

As the pandemic virus spreads to more people around the world, the diversity among clades may disappear as they mingle with each other, Nelson adds. “We’ll have to wait for the next round of data to see if it’s more mixed.”

Although researchers’ best guesses are improving as detailed molecular and genetic data and doctors’ reports pour in, divining the virus’s future is impossible.

“This is a new virus,” Palese says, but it is still subject to the same rules and regulations as other influenzas. “Never predict anything,” he says, “but I would argue that it will change like the other seasonal influenzas have in the past.”

The skinny on the bacon

The current pandemic, known to many around the world as swine flu, suffered an image problem in its early days. Misinformation led to mass slaughters of pigs in misguided attempts to halt the virus’s spread. The H1N1 virus can’t be transmitted by eating pork: The virus infects the respiratory tract of pigs, not the edible muscle or fat, and cooking deactivates the virus anyway. So the risk from eating infected pork is nil, unless pig throat sushi is on the menu, says Peter Palese, an influenza expert at Mount Sinai Medical Center in New York City.

Instead, the current H1N1 influenza travels in the same way as most seasonal flus — through the air and on virus-laden surfaces. Flu viruses hitch rides on droplets expelled from sneezes and coughs, float through the air and then infect a person when inhaled. Dry wintry conditions lead to smaller droplets, which can persist in the air for hours, Palese says.

Flu viruses can also move from person to person through contact, such as handshaking or doorknob turning. The good news is that most influenzas, including this one, are relatively fragile outside of a host. H1N1 doesn’t survive long on surfaces outside of the body and can be easily destroyed with disinfectants.

Precautions such as frequent hand washing can slow the virus’s spread,

but Palese says avoiding every tiny particle of influenza is often impossible. “The best way to prevent influenza, whatever way it’s being transmitted, is vaccines,” Palese says. “That’s the bottom line.”

To find an H1N1 vaccine, go to <http://www.flu.gov>.

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HSVT

Feb. 14, 2010 at 3:54am

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Paul Etzler

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