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NEWS OF THE WEEK

SWINE FLU OUTBREAK:

Out of Mexico? Scientists Ponder Swine Flu's Origins

Jon Cohen

Each scientist at the forefront of the current swine flu outbreak remembers the day when it became clear that this was not a typical influenza season. For Celia Alpuche, that date was 7 April, more than 2 weeks before hundreds of other scientists, doctors, secretaries of health, and even presidents would also start losing sleep over a virus now officially known as 2009 A (H1N1).

Breathing easier? Mexican officials believe the outbreak there has stabilized, reducing fears of widespread disease and death.

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Alpuche is an infectious disease microbiologist who heads the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (InDRE) in Mexico City, the country's main lab for testing influenza samples. On that Tuesday in early April, she learned that the nearby National Institute of Respiratory Diseases had severe cases of pneumonia in young adults—the age bracket that typically suffers the *least* harm from flu. "It sounded unusual," says Alpuche. "Immediately, we started to get the data around this cluster."

Alpuche and her team analyzed data on the country's influenza from this season and the one before, looking at the distributions of the virus's two strains, A and B. They noticed that this year's flu season seemed unusually long and that B cases accounted for 37% of the total, up from 15%. Surveillance data in the United States looked similar.

It turned out that the bump in influenza B had nothing to do with the swine flu outbreak, which is caused by an A strain. But it clouded Mexico's early attempts to make sense of these odd respiratory cases in young adults. "It was very confusing," says Alpuche. Nor did InDRE or other less sophisticated Mexican labs have the capability to identify a novel H1N1 strain, ultimately leading Mexico to ask Canada and the United States for assistance. "This is a new, unknown virus," she says, and those are notoriously difficult to detect. The U.S. Centers for Disease Control and Prevention (CDC) and the Public Health Agency of Canada confirmed that the novel virus was an H1N1 strain of swine flu origin on 23 April.

Since then, says Alpuche, Mexico has been "working very hard" to overcome its limitations in diagnostics and surveillance.

Alpuche and her superiors reject the assertion that Mexico, where the outbreak seems to have emerged, might have contained the virus if officials had pounced on it sooner. "I don't see any way we could have acted faster," says epidemiologist Mauricio Hernández-Ávila, the vice minister of disease prevention and health promotion for Mexico's Ministry of Health.

The exact dates remain fuzzy, but Mexico's outbreak of 2009 A (H1N1) surfaced at the earliest in mid-March, and Alpuche and colleagues had their antennae wiggling by early April. "I think the Mexicans did all that was possible with a virtually impossible situation," says Ira Longini, an epidemiologist at the University of Washington, Seattle. Longini's models of influenza pandemics have shown that it's nearly impossible for a country to contain an outbreak of a new influenza virus. "You can see what happened in the United States," says Hernández-Ávila. "They even found the virus before we did, and they were not able to contain it." (The first U.S. case was confirmed on 14 April.)

An outbreak timeline.

CREDITS: PAN AMERICAN HEALTH ORGANIZATION; PUBLIC HEALTH AGENCY OF CANADA

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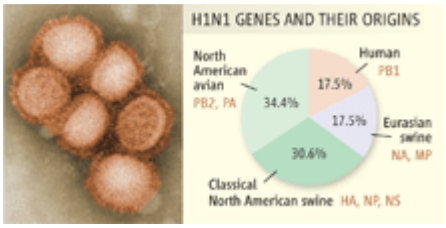
Mexico is but one player under the microscope for its early actions in this outbreak: The World Health Organization (WHO) and CDC have also received close scrutiny. And the microscope has finer resolution than ever before because of Web cast press conferences, Twitter, Facebook, YouTube, Google Maps, and Skype. Yet the same Internet-fueled technologies have helped these same people do their jobs. "I'm amazed at the capacity we have with the information and communication technologies," says epidemiologist Mirta Roses Periago,

head of the Pan American Health Organization. "We used to do things with our hands and smelling and looking at the patients." During the past few weeks, she notes, scientists have rapidly shared sequences of the viruses, digital images of patient x-rays, and electron micrographs of the new H1N1. "At this point in history, this is the best surveillance we've ever had," said Keiji Fukuda, one of WHO's assistant director generals. As of 4 May, that surveillance had confirmed more than 1000 cases in 21 countries, and WHO had raised the pandemic threat alert to phase 5, one shy of a full-blown pandemic. Phase 5 indicates that two countries in the same region (the United States and Mexico) had ongoing, person-to-person spread in communities. Although early this week there was some indication that the virus might not be as dangerous as first feared, many still expect that a phase 6 alert, which indicates the same high level of spread in two or more WHO regions, is inevitable.

The origin of the virus, its muscle power, and how much of a threat it presents remain mysteries. "We're not quite certain how this is going to evolve," said Fukuda at a 4 May press conference. Despite this uncertainty, health officials and companies are gearing up to rush a new vaccine into place, if it is needed (see p. 702); already, WHO and governments have released antiviral drugs from their stockpiles (see p. 705).

After Mexico, the United States has had the most cases, which on 5 May totaled 403. The almost simultaneous confirmations of the outbreak in both Mexico and the United States initially added further confusion to the outbreak's origins. But the virus itself has helped clear up matters, says Ruben Donis, CDC's chief of the molecular virology and vaccines branch.



Quick picture. Within a few days of isolating the virus, shown in the electron micrograph on left, CDC had a detailed genetic phylogeny.

CREDIT: SOURCE: RUBEN

DONIS; (IMAGE) CDC

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Donis has led a full-tilt effort to sequence viral isolates and post them in GenBank, a publicly available database that by 4 May had nearly 200 entries of H1N1 genes. The genetic information helps labs around the world develop diagnostic tests for this new virus, key to speeding the investigation; at first Mexico and many other countries had to rely on CDC or the Public Health Agency of Canada (*Science*, 1 May, p. 572) to confirm suspected cases.

Donis's group has used the gene sequences to tease out some of the virus's surprising history. A comparison to known influenza strains in different species shows that about one-third of the virus is from "classical" North American swine influenza, one-third is North American avian, and the remaining third is divided evenly between human and Eurasian swine (see pie chart). "It's almost equidistant to swine viruses from the United States and Eurasia," says Donis. "And it's a lonely branch there. It doesn't have any close relatives."

Some have speculated that the outbreak started from an infected pig in Mexico, as an early case occurred in a region in Veracruz state that has a large pig farm. But Donis says this explanation may be too pat. He suggests that the virus may have originated in a U.S. pig that traveled to Asia as part of the hog trade. The virus may have infected a human there, who then traveled back to North America, where the virus perfected human-to-human spread, maybe even moving from the United States to Mexico.

Alpuche notes that some of the earliest cases occurred in communities "well known for migration." And a scouring of older samples—which is ongoing—recently uncovered a Mexico City case from 11 March, about a week before any confirmed infections in Veracruz. As to what enabled this swine influenza for the first time to transmit easily between humans, Donis says the sequence alone can't answer that question.

On 2 May, Canada's Food Inspection Agency reported that 2009 A (H1N1) had been found in pigs for the first time. But in yet another twist, the virus seems to have come from a farm worker who recently returned from Mexico with a bout of swine flu and then infected the herd. This type of transmission, so far detected in 220 of the 2200 animals, may be a first, says Christopher Olsen, a swine influenza researcher at the School of Veterinary Medicine at the University of Wisconsin, Madison: "I honestly can't think of an instance where we saw a swine virus move to humans and move back in this fashion."

The greatest concern is what will this confusing virus do next? Hernández-Ávila says he believes the outbreak in Mexico has stabilized. By 4 May, fewer samples were coming into the labs and fewer patients were checking into hospitals with respiratory diseases. Earlier, the country reported a few thousand suspected cases and close to 200 deaths, but out of 2164 tested samples, labs only confirmed 727 infections and 26 fatalities.

But several experts stressed that the outbreak is still young. "I don't think we're out of the woods yet," said Anne Schuchat, CDC interim deputy director for science and public health, at a 3 May press conference. "We don't know if the virus will return in the fall and come back harder than it is right now." CDC's Donis, originally from Argentina, also notes that the United States and Mexico are in the Northern Hemisphere, where flu season has peaked. "We're in a good position," he says. "The folks in Buenos Aires are in trouble. They're entering winter now."

So while scientists and health officials in the north may soon be able to get a good night's sleep, the espresso machines in labs and government ministries in the Southern Hemisphere may soon be working overtime.

Viral itinerary. CDC's Donis worries about H1N1's next move.

CREDIT: JAMES GATHANY/CDC

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