



# *Trends-in-Medicine*

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by D. Woods

## *Quick Pulse*

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### **Trends-in-Medicine**

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### **SWINE FLU UPDATE**

On April 27, 2009, the White House declared a Public Health Emergency due to an outbreak of H1N1 flu in Mexico that spread to the U.S. and elsewhere. Initially, this flu was referred to as the swine flu or the Mexican swine flu, but pig farmers and pork producers complained about the nomenclature since the flu doesn't come from and is not spread by eating pork. Thus, the politically correct name is now the (influenza A) H1N1 flu.

The Canadian government said that the swine flu virus is believed to have infected pigs in Alberta, Canada. The government thinks that a farm worker who had recently been to Mexico got sick when he returned to Canada. On May 2, 2009, the World Health Organization (WHO) said that HIV patients are at high risk and need antivirals first. The organization also said that it fears complications if HIV and H1N1 viruses combine.

### **The problem**

The new novel H1N1 virus contains four genetic components: swine from North America, swine from Europe and Asia, a human component, and an avian component. It continues to spread, and WHO has upgraded it to a Phase 5 alert, which means that (1) there is human-to-human infection in at least two countries in one WHO region and (2) most countries are still not affected. A declaration of Phase 5 is a strong signal that a pandemic is imminent. Declaration of Phase 6, the highest level, means that a global pandemic is under way. U.S. officials have said that since the flu has already appeared here, that people should not be worried but should be prepared, not go to work if they are sick, and wash their hands a lot.

If WHO raises the pandemic to Phase 6, Rear Admiral Dr. Anne Schuchat, interim deputy director for science and public health at the CDC, said it would reflect the spread of the disease, not the severity of the disease.

*Will this turn into a pandemic?* Maybe. WHO has three criteria for a global epidemic:

1. The virus is able to infect people.
2. The virus can readily spread person-to-person.
3. The global population has no immunity to it.

*Is it as dangerous as the swine flu epidemic of 1918 (caused by a virulent influenza A H1N1 strain) in which as many as 50 million people died?* Very unlikely at this point. CDC experts have been reassured by a lack of viral mutations, but the potential for reassortment remains. The U.S. and five other countries are sharing their virus sequence data, and all of the genes examined so far are reported to be 99%-100% identical. The CDC does not see the markers for

virulence that were in the 1918 virus. On April 30<sup>th</sup> Mexico's health minister said that the number of new swine flu cases had stabilized.

As of May 3, there were 226 **confirmed** cases in 30 states, up from 160 cases in 21 states the day before. The CDC's Dr. Schuchat said the jump in numbers is "catch-up," explaining, "Part of this increase is just catching up on the testing... This virus is fairly widespread in the U.S... More people are getting flu tested, and most are recovering... Virtually all of the U.S. probably has this virus circulating now."

The highest number of cases has occurred in New York, Texas, California, Arizona, and South Carolina, but there are now cases across the U.S. About two-thirds of the Americans who contracted this flu had not been to Mexico and probably got the virus in their communities. Dr. Schuchat said, "We think that there is sustained transmission here in the U.S. in several areas."

Dr. Schuchat said states are starting to confirm their own cases, and she believes the number will go up quite a bit in the next few days, "We believe that we are just on the upswing here... I do expect more cases, more severe cases, and I do expect more deaths, and I am concerned about what will happen in the fall."

One important difference between this flu and seasonal flu is that the current hospitalizations "are older children and young adults." The people who have been hardest hit with this flu are generally not the elderly but teenagers and young adults – which is the patient population expected to be hit in a pandemic.

Thirty of these 226 flu victims were hospitalized. Some hospitalizations were described as "severe," but Dr. Schuchat said it is too soon to know the extent of the severity. So far, all Americans infected with this flu have recovered. The one victim who died in the U.S. was a Mexican child visiting relatives in Texas.

The median age of victims is 17 and ranges from 1- to 81-years-old. It is surprising that the U.S. patients appear to have a less serious disease course than the Mexicans, and there is no definitive explanation yet for this, so Americans are warned not to be "overly reassured" by that. Officials also warned that deaths of Americans are still likely.

As of May 1, 2009, 430 public and private schools had closed – <0.5% of the nearly 100,000 schools in the country. New recommendations are for schools which make the decision to close to stay closed for 14 days because children tend to shed the virus for a longer period of time than adults. An attack rate of 33% (in schools, e.g. New York City) is pretty normal. Dr. Schuchat said, "The virus spread pretty easily in those high school students. This virus is very transmissible."

### The government effort

The key U.S. officials dealing with the flu outbreak are:

- Janet Napolitano, Secretary of the Department of Homeland Security (DHS)
- Dr. Richard Besser, acting director of CDC
- Department of Health and Human Services Sec. Karen Sebelius
- John Brennan, assistant to the President for homeland security/counterterrorism
- Acting FDA commissioner Dr. Joshua Sharfstein
- Department of Health and Human Services (HHS) assistant secretary for preparedness and response Dr. Craig Vanderwagen

A new interagency, the Homeland Security Council, has been formed to coordinate flu activities among the agencies responsible for recognition, response, and communication with domestic and international partners. Conferences and decisions are reported daily to senior leaders in the federal government and the White House. Within the Homeland Security Council:

- HHS is responsible for the overall effort to coordinate disease surveillance, medical preparedness, and guidance to doctors.
- CDC is responsible for identifying and tracking spread of disease and community health related information to the government, media, and public. CDC is providing technical support on the epidemiology and has a team in Mexico trying to understand why it's more severe there. CDC is also helping Mexico establish more laboratory capacity there.
- HHS has overall leadership for coordinating the response to the flu epidemic in the U.S.

Declaring a public health emergency:

- Allowed government money to provide state and local agencies with (1) diagnostic tests such as the rRT-PCR Swine Flu Panel, which is not FDA approved, and (2) antivirals as well as N95 respirators.
- Gave the authority to give young children (under age 1) antivirals.

Acting FDA commissioner Dr. Joshua Sharfstein described the four recent emergency use authorizations:

- Both Roche's Tamiflu (oseltamivir phosphate) and Glaxo-SmithKline's Relenza (zanamivir for inhalation) can be distributed to large segments of the population without complying with the label requirements and can be distributed by health public workers and volunteers.

- Tamiflu can now be used for children as young as age one. Asked how the FDA decided to allow Tamiflu for children this young, Dr. Sharfstein said, “The FDA has been looking at this for a couple of years and working with the National Institutes of Health (NIH) and with the company to get data for children under age one. There was a study done, and over the weekend we got additional data from the company – the study involving more than 750 infants from Japan and Germany.”
- CDC is now allowed to distribute a test that can presumptively diagnose this infection. The test amplifies the viral material. Negative results do not exclude the possibility of infection. The PCR test that is being sent to the states and used in state public health labs was developed by the CDC and licensed this year. It’s called a “five target PCR test kit.”
- HHS is allowed to deploy (N95) respirators from the stockpile – the products *may* help users from getting sick.

Dr. Sharfstein added, “As soon as we became aware of this last week, I asked FDA’s acting chief scientist (Dr. Jesse Goodman) to coordinate and lead the FDA’s efforts. We have changed the way that the FDA is managed for this process, issuing an incident management approach with Dr. Goodman as the leader.”

Seven FDA teams are working with the various agencies:

- **Vaccine team:** Working to facilitate availability of a safe and effective vaccine to protect the public from the virus as soon as possible. Having that vaccine ready is the goal of the team. There is a completely different question of for whom that vaccine would be recommended, but the FDA wants to have a vaccine that is “as safe and effective as possible.” The FDA is growing the vaccine in the lab and trying to engineer a reference vaccine. It is already preparing agents to be used for testing. It is thinking about what clinical evidence is necessary. The team is working with BARDA (the Biomedical Advanced Research and Development Authority, within the Office of the Assistant Secretary for Preparedness and Response in HHS), and HHS is consulting with the vaccine industry.
- **Antiviral team:** The goal is to identify and evaluate antiviral drugs. This is the team that led the effort to review the emergency use authorizations with CDC. It is also in extensive talks with manufacturers about other options to treat infections, particularly as they become severe. This team uses its expertise to identify the right dose for children under one.
- **In vitro diagnostics team:** This team approved the test that the CDC is distributing. It is working with manufacturers on the availability of the tests.
- **Personal equipment team:** Did the mask authorization. It is in contact with key manufacturers to make sure that appropriate supplies are available and distributed.

- **Blood team:** Is dedicated to the safety and availability of blood products needed for transfusions during this outbreak. The main purpose is to make sure that there is adequate blood available. The response to this doesn’t reduce the number of donors, but they are also starting to think through whether there is any potential risk to the blood supply. So far there is nothing that the team is recommending in terms of particular controls.
- **Shortage team:** Is working with manufacturers on the issue of how to expand production of key medications and looking at spot shortages.
- **Consumer communications team:** Monitors for scams, potentially dangerous products.

### Questions and answers

#### *Is this a respiratory or gastrointestinal (GI) flu?*

The CDC’s Dr. Besser said, “The primary symptoms that we hear about are fever. Respiratory symptoms are still what people need to look for. Some have had GI symptoms of diarrhea and vomiting, and if you have those symptoms, it doesn’t rule out that this could be swine flu. Some have reported that.”

#### *What do you do if a case of the flu is suspected?*

Doctors have been asked to take a nose swab and send it to a local lab for testing. The CDC plans to release new guidance soon for clinicians about testing and treatment.

People have been asked to stay at home if they – or anyone in their household – come down with flu symptoms. The state public health labs and some large city public health labs have the new testing kits dispensed by the government. Labs at state public health laboratories reportedly are operating at full capacity, but in the last several days the CDC shipped out new H1N1 virus kits to the labs, and they are starting to confirm the new strain themselves.

#### *How effective are the antivirals like Tamiflu?*

The CDC’s Dr. Besser said that is not known yet. He also said that the CDC needs to undertake some studies first.

#### *Are there plans for the government to mount a vaccine program for this swine flu?*

Yes, the government is in discussions with the vaccine manufacturers.

#### *What is the manufacturing capacity for a swine flu vaccine since this is not the normal flu season? How will a new swine vaccine impact preparedness for next winter’s flu season? How is manufacturing capacity impacted because of the timing?*

The government is looking at the severity of the strain and its sustainability in the community and has to decide whether the

vaccine will be stand-alone or included in the seasonal vaccine, which is already being manufactured. Currently, vaccine manufacturers are working on a seasonal flu vaccine which contains 3 types of antigens. The government and the vaccine manufacturers are discussing whether a fourth antigen can be added or whether there needs to be a substitution or change in production.

#### ***Is there still a concern about avian (bird) flu?***

Yes, and the U.S. government is supporting development of a diagnostic test for avian flu. CDC and the Office of Public Health and Emergency Preparedness at HHS have partnered to co-manage the development of diagnostic tests for avian influenza (H5N1). In March 2009, the CDC said that it had awarded \$11.4 million in new contracts to four *in vitro* diagnostics (IVD) companies for developing rapid diagnostic tests for avian influenza: \$2.4 million to Cepheid, \$3.8 million to Iqum, \$706,241 to Meso Scale Discovery, and \$4.5 million to Nanogen.

Nanogen, the recipient of the most funding for the first two phases, is working to develop a high-sensitivity lateral-flow test using the underlying technology employed in its current cardiac infarction products. According to Suzanne Clancy, PhD, Nanogen's director of corporate communications, "We plan to capitalize on current technology to develop a readily adaptable test that can provide results at the point of care in as few as 15 minutes."

#### ***What is going on at the state level?***

States are activating their pandemic influenza plans. The original plans predicted that any pandemic virus would originate outside of the U.S., so the states are working with the CDC to modify the plan. As of August 2008, the states did not have any more money for pandemic planning. Dr. Paul Jarris, executive director of the Association of State and Territorial Health Officials, said, "We don't have a preparedness force ready and waiting for a pandemic or floods or hurricanes. This is the regular public workforce." He said that states are vulnerable in the area of public health worker "boots on the ground."

In addition to the current \$600 million for state and local governments, Dr. Jarris said that they need an additional \$350 million. State stockpiles are short 8 million courses of antivirals, and states need an additional \$122 million to bring state stockpiles up to benchmark goals. States are also asking for another \$563 million to buy personal healthcare equipment for healthcare workers. This is in addition to a requested \$350 million more for preparedness and in addition to the current \$600 million in the budget.

Sen. Tom Harkin of Iowa, chair of the Labor, Health, and Human Services subcommittee of the Senate Appropriations Committee, said that it is obvious that the states need more money to deal with a pandemic, "It is crystal clear that the public health departments in state governments have been

inadequately funded in the past, and they seem to be first-cut in budgets, and when something like this (outbreak) rears its ugly head, we find that we are not as prepared as we could be...I remain deeply concerned about their ability to rapidly answer a growing pandemic in some areas of some states... We have to strengthen the public health sector, both state, local, and national."

#### ***How long will it take to make a vaccine effective against this H1N1 flu?***

After the seed strain is sent to manufacturers, pilot lots are made in order to determine the right dose. The pilot lot process can take up to eight weeks, and it can be simultaneously ramped up for production. A number of doses can be off the assembly line in 4-6 months.

#### ***When might a vaccine for this H1N1 flu be available?***

Vaccine manufacturers already have produced "a great deal" of the vaccine for the next flu season. Some vaccine manufacturers are further ahead than others. Some have had difficulty in growing the influenza B vaccine, which was updated.

The FDA's Dr. Sharfstein said:

- In 2004 there weren't enough extra eggs, but HHS has contracted extra flocks, and there is now year round egg available. The FDA has also solicited other companies to make the vaccine for the U.S. market and used the accelerated approval approach to bring online three new factories.
- The capacity this year is 130-140 million doses instead of the 60 million in 2004, with additional potential manufacturing capacity. "All the companies are engaged with us on how to make a vaccine."
- We now have the capacity to have 200,000 eggs a day and as much as 500,000 eggs a day year round.
- The basic infrastructure is in place to make a vaccine. The problem is the unpredictability of the virus itself and potential problems growing and testing it.

#### ***What is the progress with cell-based vaccine development?***

Dr. Sharfstein said, "Because we have a licensed process for an egg-based vaccine and because we have the eggs, we have tremendous capacity to make vaccine with the egg-based approach."

#### ***How might manufacturing be affected if the outbreak turns into a pandemic?***

Dr. Sharfstein said, "We have been having discussions with (cell-based vaccine manufacturers), and that is the future." HHS's Dr. Vanderwagen added, "I wouldn't rule out that it's in the future for this particular strain...and the potential (for egg-based) is larger than 160 million doses. Those are the trivalent vaccine, so it's probably somewhere around triple that...I think that 300 million doses is achievable in a six-



month time frame in egg-based with some cell-based augmentation...We have large plants at a very late stage of construction which are close to inspection, and we've made significant progress with them. Will they be ready by January (2010)? I don't know, but in existing structures we could produce 600 million doses in a six-month time frame."

### The facts, not rumors and myths

There has been a lot of misinformation circulating about this flu outbreak. Here are some key **facts** from government officials.

- There has been no evidence this is bioterrorism, and that possibility was investigated. A White House official said, "There is no evidence whatsoever that we've seen" that the outbreak might be related to bioterrorism.
- Even if cases start to taper off, they could come back again in the fall.
- The U.S. government is recommending that **non-essential** travel to Mexico be avoided. Dr. Besser said it is "premature to put travel restrictions on people coming to the U.S." The U.S. embassy in Mexico City and consulates have suspended all non-essential services to the public until at least May 6<sup>th</sup>.
- Surveillance at the borders is **passive**. DHS Sec. Napolitano said, "Right now, we don't think that the facts warrant a more active testing or screening of passengers coming in (to the U.S.) from Mexico...but this is a changing dynamic that we may increase or decrease as the facts change...People will be processed through appropriate Customs and Border Protection (CBP) protocols. Right now it's passive. They ask if you are sick, have you been sick, and they (if they answer yes, they) can be referred over for further examination. Passengers presenting with symptoms will be isolated per established rules and will be provided with personal protective equipment, and we will be emphasizing hand washing and gloves."
  - The Transportation Security Administration (TSA) has similar measures.
  - The U.S. is distributing yellow cards at ports of entry describing swine flu and explaining how to avoid it and prevent the spread.
  - Officials rejected a suggestion of taking the temperature of people crossing the U.S.-Mexico border, saying that it wouldn't work.
  - The CDC continues to say that scientific evidence (including a 2007 analysis) shows that closing a border would not be worth the investment/cost. The government focus is not on closing the border; it is on mitigation.
- People should **not** get tested **in the absence of symptoms**.
- This flu was thought to have a 24-hour incubation period, but officials have revised that and are now saying the incubation period is one to five, seven, or even 14 days. When there is a case of swine flu in a community, people are advised to stay home as much as possible – not go out – for 7 days and if they do go out, to stay out of crowded places. Schools may be closed as a precaution and community and other functions cancelled.
- The existing flu vaccines are **not** considered effective against this outbreak.
- Two antivirals – Tamiflu and Relenza – are thought to work against this strain, but they both must be taken within a day or two of onset. This flu strain is resistant to amantadine and rimantadine.
- The government released 25% of the 50 million doses in the "Strategic National Stockpile" of anti-flu drugs, like Tamiflu, to deal with this outbreak. Government officials believe there are sufficient antiviral supplies to meet demand right now.
  - The Defense Department got an additional 7 million doses.
  - Doses were shipped where they were most needed, not equally to each state.
  - The states have another 23 million courses.
  - The U.S. is replenishing its stockpile with existing funds. It probably has enough existing funds to cover the antivirals already sent to the states. However, "It will be a difficult challenge to find funding within the existing HHS appropriations. NIH will conduct clinical studies for safety and efficacy in partnership with the FDA and will begin to look at developing the pilot lots, in addition to trying to ramp up additional production capacity."
  - HHS has begun purchasing an additional 13 million regimens of antivirals.
- WHO has its own stockpile of antivirals – 150 million courses. The U.S. has not received requests from other countries for Tamiflu.
- The government is working with vaccine manufactures on a vaccine.
  - Officials are discussing with vaccine manufacturers whether they can add a 4<sup>th</sup> strain to the winter flu vaccine they are currently gearing up to make – or whether they will have to substitute one of the 3 strains already planned for the winter vaccine.
  - The CDC does have the "seed stock" for a swine flu vaccine. It turned over its seed strain to an academic laboratory which is responsible for the reverse genetics process.

- Existing manufacturing plants can produce 600 million doses in a six-month time frame. Two new plants for producing cell-based vaccines are nearing the final stages of completion.
  - Baxter Pharmaceuticals said that it will receive seed stock soon. Baxter said that it will take three to four weeks to evaluate the strain before it can start manufacturing a vaccine. If the strain is similar to strains that Baxter has used, first doses will be available 12 to 16 weeks after manufacturing begins. Baxter doesn't know whether it has to interrupt manufacturing of its regular seasonal flu vaccine.
- The Department of Agriculture is monitoring and testing to make sure there are no problems with the food supply. So far, "everything looks fine." Livestock are also being screened and tested.
  - Businesses are advised to have a plan – what to do if some workers couldn't come to work.
  - CDC does not recommend people wearing masks in the workplace as a precautionary measure; their value outside of healthcare settings has not been established.
  - The White House is asking Congress for \$1.5 billion in emergency supplemental funding to fight the outbreak. Asked about what the \$1.5 billion is for, HHS's Dr. Vanderwagen said, "We are looking at the cost of production of vaccine, potential medical supplies should we have wider, more severe spread, and when we look at a number of those issues, this was a place to start. The majority would be for looking at additional medications, additional development costs associated with the vaccine, and providing support to local communities and states for preparedness. The universe of need could be quite large – much larger than that (\$1.5 billion) figure."

Asked how much of the \$1.5 billion would go to the states, Dr. Schuchat said, "These are being evaluated, and OMB (Office of Management and Budget) is going to submit something soon." Cong. John Dingell of Michigan responded, "In other words, you don't know." Cong. Dingell then asked all three witnesses to submit their budget structures to the committee.

- Nothing identifies swine flu from any seasonal flu, except an examination of the genome sequence.
- Mexican health officials say that the two earliest known cases occurred in the states of Oaxaca and Veracruz. On April 12, a 39-year-old woman in Oaxaca was taken to the hospital with a severe case of pneumonia. She died 24 days later. Health officials said that her biopsy showed an unknown virus, a sample was submitted to the CDC and a Canadian health lab which on April 23 matched it to a virus found in two California cases. There was a known flu outbreak in the small community of Perote, Veracruz, in mid-April 2009. A four-year-old boy, who recuperated, was the only one to test positive for swine flu.

### Other interesting information

Veratect was the first organization to notify the CDC of the swine flu outbreak in Mexico. Veratect tracks thousands of events every month (not just flu). It started tracking "disruptive events" in early April, found the first indicators in Mexico, and the company was the first to alert CDC and its global disease tracking center, which was unaware of the outbreak. Veratect CEO Bob Hart said, "We provided detection beginning on April 6<sup>th</sup>, and we freely provided access to the WHO, Pan American Health Organization, and CDC. On April 16, Veratect saw an increase in signals in Mexico and emailed an early warning alert to the CDC and the global disease detection team."

Hart likened his company to a forest fire watch tower looking for wisps of smoke before they turn into a full fledged fire – and giving people and governments an opportunity to react earlier rather than afterwards to repair and restore and rescue. As for the swine flu outbreak, he said, "We think that this is a very serious event, and we're very concerned, but we're not in the business of forecasting this."

As for the internet rumors pointing to the Smithfield pig plant near La Gloria, Mexico, as the source, Hart said, "We have not seen anything that says that Smithfield was involved." He said that often locals will try to point to a source for disease, and the plant "sent up a flare," adding, "We do know that influenzas often originate in pigs, sometimes birds, and close proximity to those animals, especially in the third world, is a mechanism by which the virus can make that jump from an animal to people...While there is a Smithfield plant there, unfortunately there is close proximity between living quarters in parts of Mexico and lots of pigs...There is nothing to confirm a relationship."

Hart said that there is always uncertainty about case counts until public health officials move in to investigate, and that's when there is clarity and numbers. He warned that rumors are easy to start, especially on the internet.

### Websites worth visiting include:

- <http://biosurveillance.typepad.com/biosurveillance/2009/04/swine-flu-in-mexico-timeline-of-events.html>
- If you twitter, you might follow Veratect and CDC Emergency.
- [www.cdc.gov/h1n1flu/](http://www.cdc.gov/h1n1flu/)
- CDC's educational messages are spreading virally, with 8 million daily visitors to the CDC website and more than 80,000 subscribers to twitter, with one tweet per second related to the new virus.

