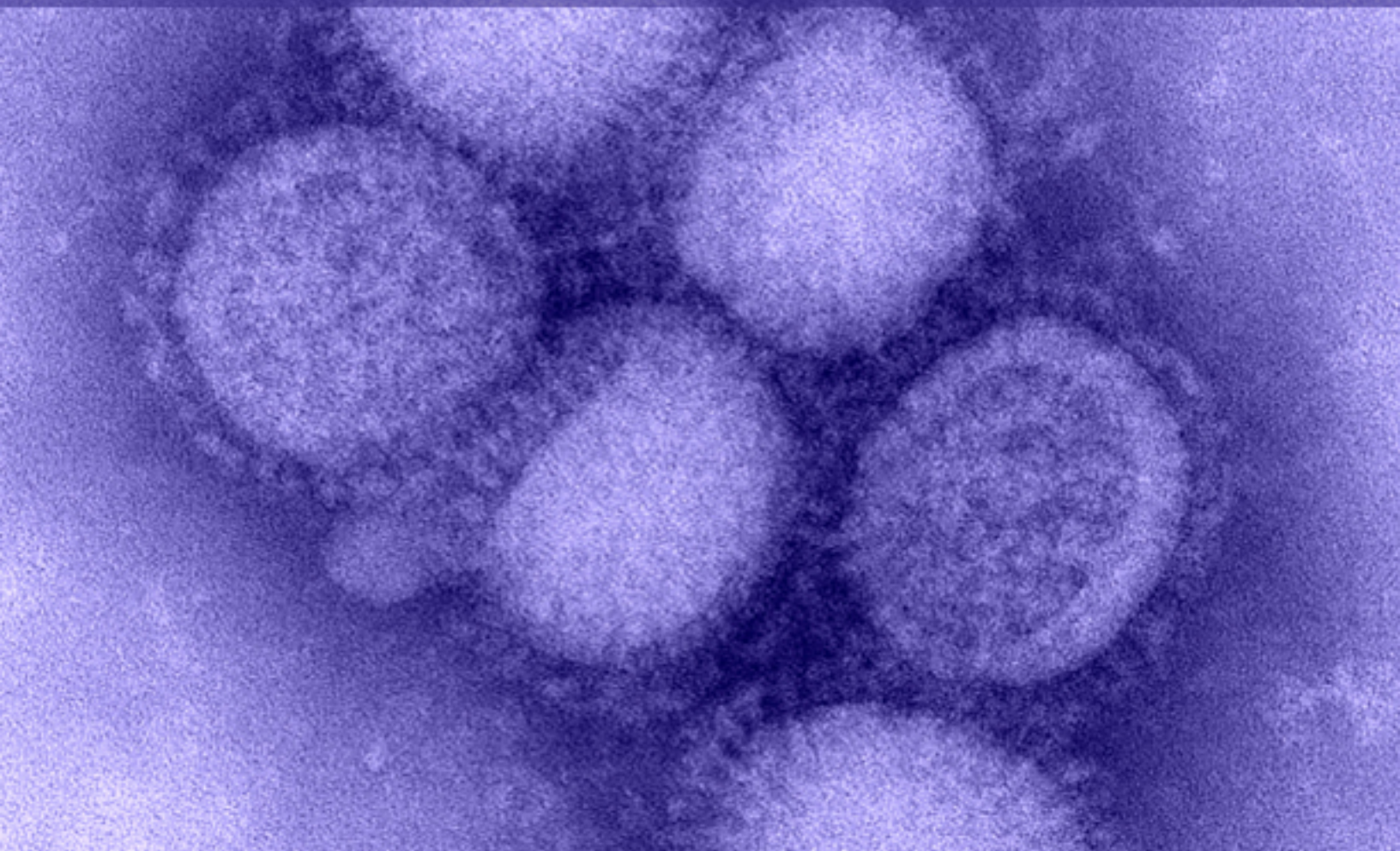


Swine Flu & Bird Flu



Daren Pease
Jaquan Winn

First Edition, 2012

ISBN 978-81-323-1435-6

© All rights reserved.

Published by:

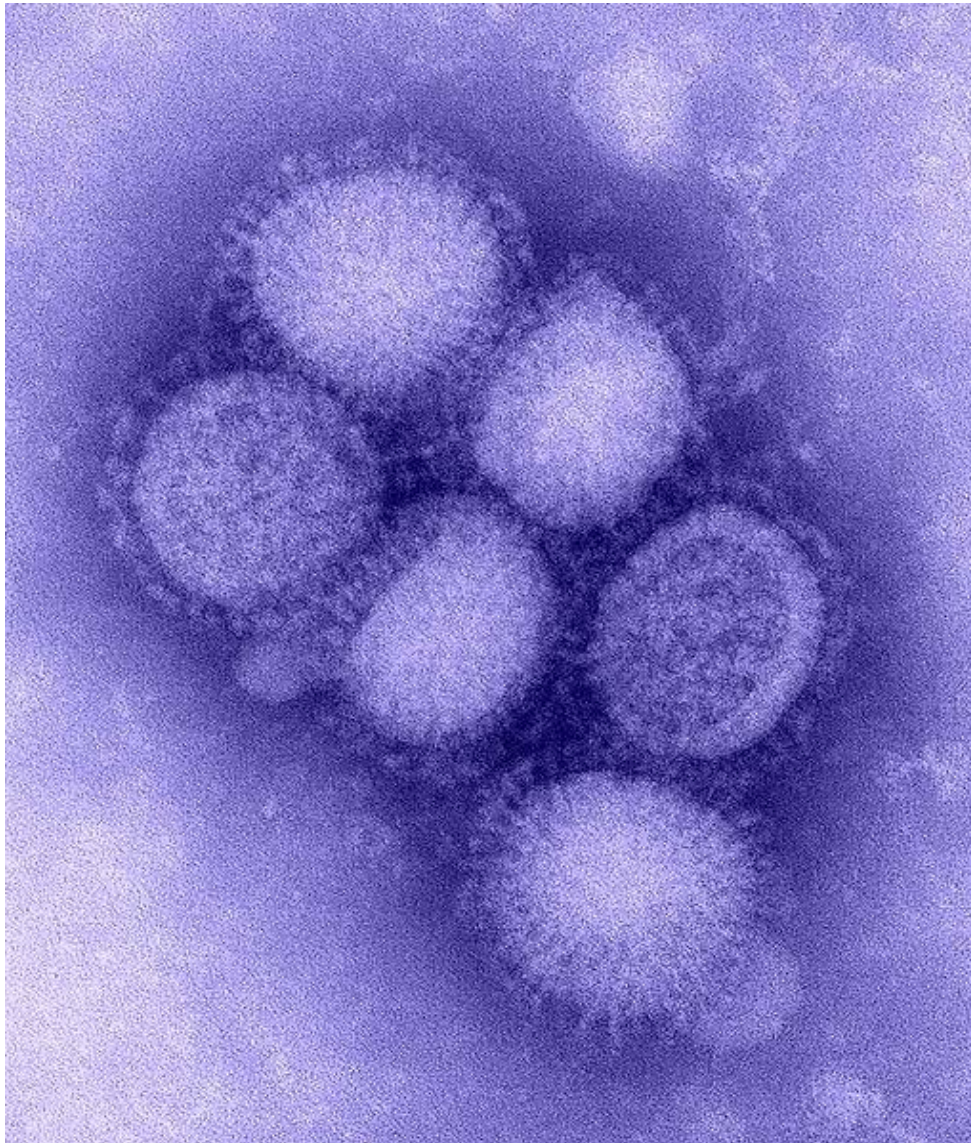
College Publishing House
4735/22 Prakashdeep Bldg,
Ansari Road, Darya Ganj,
Delhi - 110002
Email: info@wtbooks.com

Table of Contents

- Chapter 1 - Swine Influenza
- Chapter 2 - Influenza A Virus Subtype H1N1
- Chapter 3 - 2009 Flu Pandemic
- Chapter 4 - Pandemic H1N1/09 Virus
- Chapter 5 - 2009 Flu Pandemic by Country
- Chapter 6 - 2009 Flu Pandemic Vaccine
- Chapter 7 - Avian Influenza
- Chapter 8 - Influenza A Virus
- Chapter 9 - Influenza A Virus Subtype H5N1
- Chapter 10 - Transmission and Infection of H5N1
- Chapter 11 - Global Spread of H5N1
- Chapter 12 - Global Spread of H5N1 in 2004 & 2005
- Chapter 13 - Global Spread of H5N1 in 2006
- Chapter 14 - Global Spread of H5N1 in 2007

Chapter 1

Swine Influenza



Electron microscope image of the reassorted H1N1 influenza virus photographed at the CDC Influenza Laboratory. The viruses are 80–120 nanometres in diameter.

Swine influenza, also called **pig influenza**, **swine flu**, **hog flu** and **pig flu**, is an infection by any one of several types of swine influenza virus. **Swine influenza virus (SIV)** or **S-OIV (swine-origin influenza virus)** is any strain of the influenza family of viruses that is endemic in pigs. As of 2009, the known SIV strains include influenza C and the subtypes of influenza A known as **H1N1**, H1N2, H3N1, H3N2, and H2N3.

Swine influenza virus is common throughout pig populations worldwide. Transmission of the virus from pigs to humans is not common and does not always lead to human influenza, often resulting only in the production of antibodies in the blood. If transmission does cause human influenza, it is called zoonotic swine flu. People with regular exposure to pigs are at increased risk of swine flu infection. The meat of an infected animal poses no risk of infection when properly cooked.

During the mid-20th century, identification of influenza subtypes became possible, allowing accurate diagnosis of transmission to humans. Since then, only 50 such transmissions have been confirmed. These strains of swine flu rarely pass from human to human. Symptoms of zoonotic swine flu in humans are similar to those of influenza and of influenza-like illness in general, namely chills, fever, sore throat, muscle pains, severe headache, coughing, weakness and general discomfort.

In August 2010 the World Health Organization declared the swine flu pandemic officially over.

Classification

Of the three genera of influenza viruses that cause human flu, two also cause influenza in pigs, with influenza A being common in pigs and influenza C being rare. Influenza B has not been reported in pigs. Within influenza A and influenza C, the strains found in pigs and humans are largely distinct, although because of reassortment there have been transfers of genes among strains crossing swine, avian, and human species boundaries.

Influenza C

Influenza C viruses infect both humans and pigs, but do not infect birds. Transmission between pigs and humans have occurred in the past. For example, influenza C caused small outbreaks of a mild form of influenza amongst children in Japan and California. Because of its limited host range and the lack of genetic diversity in influenza C, this form of influenza does not cause pandemics in humans.

Influenza A

Swine influenza is known to be caused by influenza A subtypes H1N1, H1N2, H2N3, H3N1, and H3N2. In pigs, three influenza A virus subtypes (H1N1, H1N2, and H3N2) are the most common strains worldwide. In the United States, the H1N1 subtype was exclusively prevalent among swine populations before 1998; however, since late August 1998, H3N2 subtypes have been isolated from pigs. As of 2004, H3N2 virus isolates in

US swine and turkey stocks were triple reassortants, containing genes from human (HA, NA, and PB1), swine (NS, NP, and M), and avian (PB2 and PA) lineages.

Surveillance

Although there is no formal national surveillance system in the United States to determine what viruses are circulating in pigs, there is an informal surveillance network in the United States that is part of a world surveillance network.

Veterinary medical pathologist, Tracey McNamara, set up a national disease surveillance system in zoos because the zoos do active disease surveillance and many of the exotic animals housed there have broad susceptibilities. Many species fall below the radar of any federal agencies (including dogs, cats, pet prairie dogs, zoo animals, and urban wildlife), even though they may be important in the early detection of human disease outbreaks.

History

Swine influenza was first proposed to be a disease related to human influenza during the 1918 flu pandemic, when pigs became sick at the same time as humans. The first identification of an influenza virus as a cause of disease in pigs occurred about ten years later, in 1930. For the following 60 years, swine influenza strains were almost exclusively H1N1. Then, between 1997 and 2002, new strains of three different subtypes and five different genotypes emerged as causes of influenza among pigs in North America. In 1997–1998, H3N2 strains emerged. These strains, which include genes derived by reassortment from human, swine and avian viruses, have become a major cause of swine influenza in North America. Reassortment between H1N1 and H3N2 produced H1N2. In 1999 in Canada, a strain of H4N6 crossed the species barrier from birds to pigs, but was contained on a single farm.

The H1N1 form of swine flu is one of the descendants of the strain that caused the 1918 flu pandemic. As well as persisting in pigs, the descendants of the 1918 virus have also circulated in humans through the 20th century, contributing to the normal seasonal epidemics of influenza. However, direct transmission from pigs to humans is rare, with only 12 recorded cases in the U.S. since 2005. Nevertheless, the retention of influenza strains in pigs after these strains have disappeared from the human population might make pigs a reservoir where influenza viruses could persist, later emerging to reinfect humans once human immunity to these strains has waned.

Swine flu has been reported numerous times as a zoonosis in humans, usually with limited distribution, rarely with a widespread distribution. Outbreaks in swine are common and cause significant economic losses in industry, primarily by causing stunting and extended time to market. For example, this disease costs the British meat industry about £65 million every year.

1918 pandemic in humans

The 1918 flu pandemic in humans was associated with H1N1 and influenza appearing in pigs; this may reflect a zoonosis either from swine to humans, or from humans to swine. Although it is not certain in which direction the virus was transferred, some evidence suggests that, in this case, pigs caught the disease from humans. For instance, swine influenza was only noted as a new disease of pigs in 1918, after the first large outbreaks of influenza amongst people. Although a recent phylogenetic analysis of more recent strains of influenza in humans, birds, and swine suggests that the 1918 outbreak in humans followed a reassortment event within a mammal, the exact origin of the 1918 strain remains elusive. It is estimated that anywhere from 50 to 100 million people were killed worldwide.

1976 U.S. outbreak

On February 5, 1976, in the United States an army recruit at Fort Dix said he felt tired and weak. He died the next day and four of his fellow soldiers were later hospitalized. Two weeks after his death, health officials announced that the cause of death was a new strain of swine flu. The strain, a variant of H1N1, is known as A/New Jersey/1976 (H1N1). It was detected only from January 19 to February 9 and did not spread beyond Fort Dix.



U.S. president Ford receives swine flu vaccination

This new strain appeared to be closely related to the strain involved in the 1918 flu pandemic. Moreover, the ensuing increased surveillance uncovered another strain in circulation in the U.S.: A/Victoria/75 (H3N2) spread simultaneously, also caused illness, and persisted until March. Alarmed public-health officials decided action must be taken to head off another major pandemic, and urged President Gerald Ford that every person in the U.S. be vaccinated for the disease.

The vaccination program was plagued by delays and public relations problems. On October 1, 1976, immunizations began and three senior citizens died soon after receiving their injections. This resulted in a media outcry that linked these deaths to the immunizations, despite the lack of any proof that the vaccine was the cause. According to science writer Patrick Di Justo, however, by the time the truth was known—that the

deaths were not proven to be related to the vaccine—it was too late. "The government had long feared mass panic about swine flu—now they feared mass panic about the swine flu vaccinations." This became a strong setback to the program.

There were reports of Guillain-Barré syndrome, a paralyzing neuromuscular disorder, affecting some people who had received swine flu immunizations. Although if a link exists is still not clear, this syndrome may be a rare side-effect of influenza vaccines. As a result, Di Justo writes that "the public refused to trust a government-operated health program that killed old people and crippled young people." In total, 48,161,019 Americans, or just over 22% of the population, had been immunized by the time the National Influenza Immunization Program (NIIP) was effectively halted on December 16, 1976.

Overall, there were 1098 cases of Guillain-Barré Syndrome (GBS) recorded nationwide by CDC surveillance, 532 of which occurred after vaccination and 543 before vaccination. There are about one to two cases of GBS per 100,000 people every year, whether or not people have been vaccinated. The vaccination program seems to have increased this normal risk of developing GBS by about to one extra case per 100,000 vaccinations. The CDC states that most studies on modern influenza vaccines have seen no link with GBS, Although one review gives an incidence of about one case per million vaccinations.

1988 zoonosis

In September 1988, a swine flu virus killed one woman and infected others. 32-year old Barbara Ann Wieners was eight months pregnant when she and her husband, Ed, became ill after visiting the hog barn at a county fair in Walworth County, Wisconsin. Barbara died eight days later, after developing pneumonia. The only pathogen identified was an H1N1 strain of swine influenza virus. Doctors were able to induce labor and deliver a healthy daughter before she died. Her husband recovered from his symptoms.

Influenza-like illness (ILI) was reportedly widespread among the pigs exhibited at the fair. Of the 25 swine exhibitors aged 9 to 19 at the fair, 19 tested positive for antibodies to SIV, but no serious illnesses were seen. The virus was able to spread between people, since 1-3 health care personnel who had cared for the pregnant woman developed mild influenza-like illnesses, and antibody tests suggested that they had been infected with swine flu. However, there was no community outbreak.

1998 US outbreak in swine

In 1998, swine flu was found in pigs in four U.S. states. Within a year, it had spread through pig populations across the United States. Scientists found that this virus had originated in pigs as a recombinant form of flu strains from birds and humans. This outbreak confirmed that pigs can serve as a crucible where novel influenza viruses emerge as a result of the reassortment of genes from different strains. Genetic

components of these 1998 triple-hybrid stains would later form six out of the eight viral gene segments in the 2009 flu outbreak.

2007 Philippine outbreak in swine

On August 20, 2007, the Department of Agriculture officers investigated the outbreak (epizootic) of swine flu in Nueva Ecija and Central Luzon, Philippines. The mortality rate is less than 10% for swine flu, unless there are complications like hog cholera. On July 27, 2007, the Philippine National Meat Inspection Service (NMIS) raised a hog cholera "*red alert*" warning over Metro Manila and 5 regions of Luzon after the disease spread to backyard pig farms in Bulacan and Pampanga, even if these tested negative for the swine flu virus.

2010 Northern Ireland outbreak in swine

Since November of 2010, there have been 14 reported deaths as a result of swine flu in Northern Ireland. The majority of the victims were reported to have pre-existing health conditions which had lowered the patients' immune system. This closely corresponds to the 19 patients that had died in the year prior due to swine flu where 18 of the 19 were determined to have lowered immune systems. Because of this, many mothers whom have just given birth are strongly encouraged to get a flu shot because their immune systems are vulnerable. Also, studies have shown that people between the ages of 15 and 44 have the highest rate of infection. Although most people now recover, having any conditions that lower ones immune system increases the risk of having the flu become potentially lethal. In Northern Ireland now, approximately 56% of all people under 65 that are entitled to the vaccine have gotten the shot and the outbreak is said to be under control.

Transmission

Transmission between pigs

Influenza is quite common in pigs, with about half of breeding pigs having been exposed to the virus in the US. Antibodies to the virus are also common in pigs in other countries.

The main route of transmission is through direct contact between infected and uninfected animals. These close contacts are particularly common during animal transport. Intensive farming may also increase the risk of transmission, as the pigs are raised in very close proximity to each other. The direct transfer of the virus probably occurs either by pigs touching noses, or through dried mucus. Airborne transmission through the aerosols produced by pigs coughing or sneezing are also an important means of infection. The virus usually spreads quickly through a herd, infecting all the pigs within just a few days. Transmission may also occur through wild animals, such as wild boar, which can spread the disease between farms.

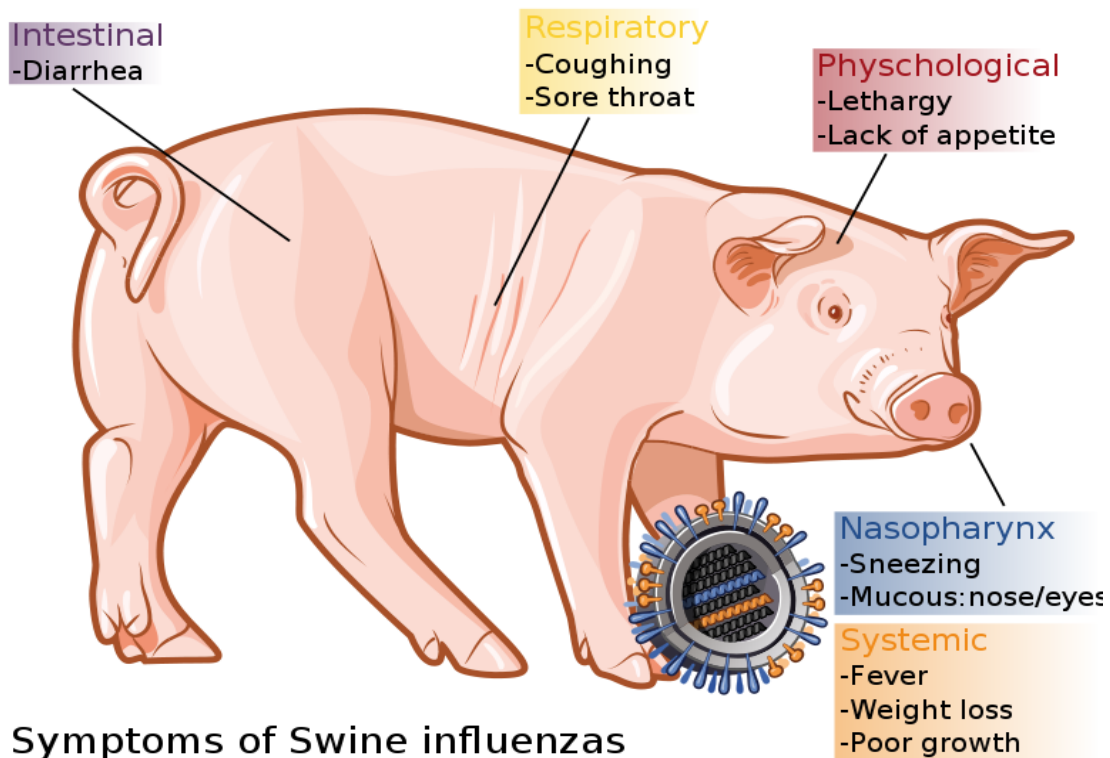
Transmission to humans

People who work with poultry and swine, especially people with intense exposures, are at increased risk of zoonotic infection with influenza virus endemic in these animals, and constitute a population of human hosts in which zoonosis and reassortment can co-occur. Vaccination of these workers against influenza and surveillance for new influenza strains among this population may therefore be an important public health measure.

Transmission of influenza from swine to humans who work with swine was documented in a small surveillance study performed in 2004 at the University of Iowa. This study among others forms the basis of a recommendation that people whose jobs involve handling poultry and swine be the focus of increased public health surveillance. Other professions at particular risk of infection are veterinarians and meat processing workers, although the risk of infection for both of these groups is lower than that of farm workers.

Interaction with avian H5N1 in pigs

Pigs are unusual as they can be infected with influenza strains that usually infect three different species: pigs, birds and humans. This makes pigs a host where influenza viruses might exchange genes, producing new and dangerous strains. Avian influenza virus H3N2 is endemic in pigs in China and has been detected in pigs in Vietnam, increasing fears of the emergence of new variant strains. H3N2 evolved from H2N2 by antigenic shift. In August 2004, researchers in China found H5N1 in pigs.



Main symptoms of swine flu in swine

These H5N1 infections may be quite common: in a survey of 10 apparently healthy pigs housed near poultry farms in West Java, where avian flu had broken out, five of the pig samples contained the H5N1 virus. The Indonesian government has since found similar results in the same region. Additional tests of 150 pigs outside the area were negative.

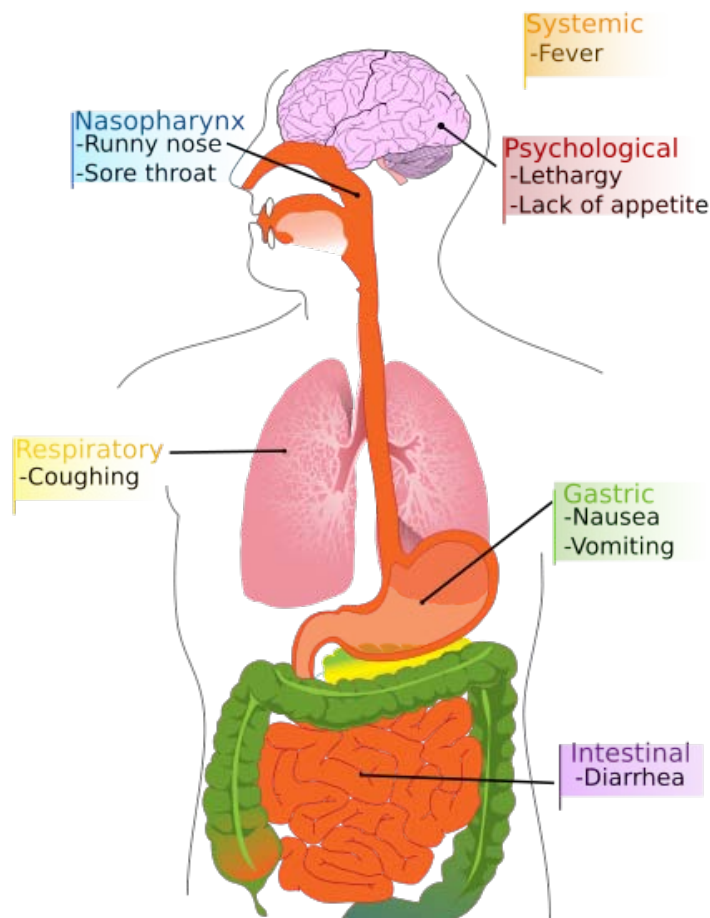
Signs and symptoms

In swine

In pigs influenza infection produces fever, lethargy, sneezing, coughing, difficulty breathing and decreased appetite. In some cases the infection can cause abortion. Although mortality is usually low (around 1–4%), the virus can produce weight loss and poor growth, causing economic loss to farmers. Infected pigs can lose up to 12 pounds of body weight over a 3 to 4 week period.

In humans

Symptoms of Swine Flu



Main symptoms of swine flu in humans

Direct transmission of a swine flu virus from pigs to humans is occasionally possible (called zoonotic swine flu). In all, 50 cases are known to have occurred since the first report in medical literature in 1958, which have resulted in a total of six deaths. Of these six people, one was pregnant, one had leukemia, one had Hodgkin disease and two were known to be previously healthy. Despite these apparently low numbers of infections, the true rate of infection may be higher, since most cases only cause a very mild disease, and will probably never be reported or diagnosed.

According to the Centers for Disease Control and Prevention (CDC), in humans the symptoms of the 2009 "swine flu" H1N1 virus are similar to those of influenza and of influenza-like illness in general. Symptoms include fever, cough, sore throat, body aches, headache, chills and fatigue. The 2009 outbreak has shown an increased percentage of patients reporting diarrhea and vomiting. The 2009 H1N1 virus is not zoonotic swine flu, as it is not transmitted from pigs to humans, but from person to person.

Because these symptoms are not specific to swine flu, a differential diagnosis of *probable* swine flu requires not only symptoms but also a high likelihood of swine flu due to the person's recent history. For example, during the 2009 swine flu outbreak in the United States, CDC advised physicians to "consider swine influenza infection in the differential diagnosis of patients with acute febrile respiratory illness who have either been in contact with persons with confirmed swine flu, or who were in one of the five U.S. states that have reported swine flu cases or in Mexico during the 7 days preceding their illness onset." A diagnosis of *confirmed* swine flu requires laboratory testing of a respiratory sample (a simple nose and throat swab).

The most common cause of death is respiratory failure. Other causes of death are pneumonia (leading to sepsis), high fever (leading to neurological problems), dehydration (from excessive vomiting and diarrhea), electrolyte imbalance and kidney failure. Fatalities are more likely in young children and the elderly.

Diagnosis



Thermal scanning of passengers arriving at Singapore Changi airport

The CDC recommends real time RT-PCR as the method of choice for diagnosing H1N1. This method allows a specific diagnosis of novel influenza (H1N1) as opposed to seasonal influenza. Near-patient point of care tests are in development.

Prevention

Prevention of swine influenza has three components: prevention in swine, prevention of transmission to humans, and prevention of its spread among humans.

In swine

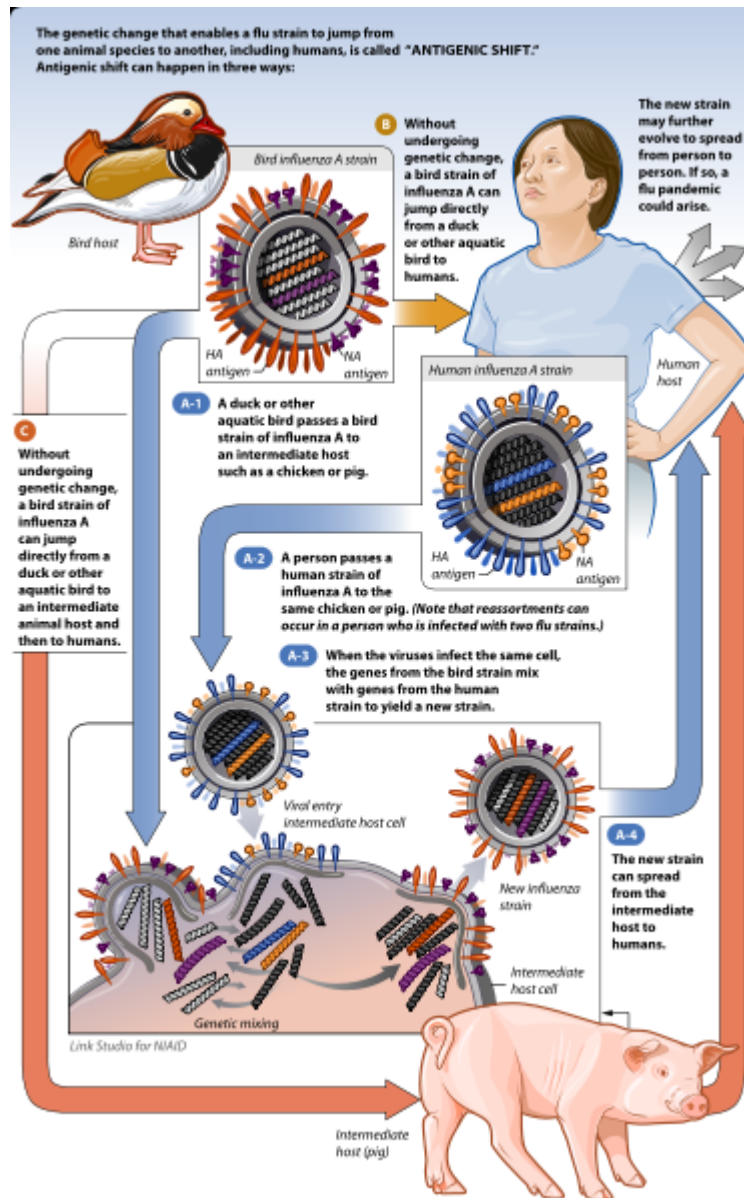
Methods of preventing the spread of influenza among swine include facility management, herd management, and vaccination (ATCvet code: QI09AA03). Because much of the illness and death associated with swine flu involves secondary infection by other pathogens, control strategies that rely on vaccination may be insufficient.

Control of swine influenza by vaccination has become more difficult in recent decades, as the evolution of the virus has resulted in inconsistent responses to traditional vaccines. Standard commercial swine flu vaccines are effective in controlling the infection when the virus strains match enough to have significant cross-protection, and custom (autogenous) vaccines made from the specific viruses isolated are created and used in the more difficult cases. Present vaccination strategies for SIV control and prevention in swine farms typically include the use of one of several bivalent SIV vaccines commercially available in the United States. Of the 97 recent H3N2 isolates examined, only 41 isolates had strong serologic cross-reactions with antiserum to three commercial SIV vaccines. Since the protective ability of influenza vaccines depends primarily on the closeness of the match between the vaccine virus and the epidemic virus, the presence of nonreactive H3N2 SIV variants suggests that current commercial vaccines might not effectively protect pigs from infection with a majority of H3N2 viruses. The United States Department of Agriculture researchers say that while pig vaccination keeps pigs from getting sick, it does not block infection or shedding of the virus.

Facility management includes using disinfectants and ambient temperature to control virus in the environment. The virus is unlikely to survive outside living cells for more than two weeks, except in cold (but above freezing) conditions, and it is readily inactivated by disinfectants. Herd management includes not adding pigs carrying influenza to herds that have not been exposed to the virus. The virus survives in healthy carrier pigs for up to 3 months and can be recovered from them between outbreaks. Carrier pigs are usually responsible for the introduction of SIV into previously uninfected herds and countries, so new animals should be quarantined. After an outbreak, as immunity in exposed pigs wanes, new outbreaks of the same strain can occur.

In humans

Prevention of pig to human transmission



Swine can be infected by both avian and human influenza strains of influenza, and therefore are hosts where the antigenic shifts can occur that create new influenza strains.

The transmission from swine to human is believed to occur mainly in swine farms where farmers are in close contact with live pigs. Although strains of swine influenza are usually not able to infect humans this may occasionally happen, so farmers and veterinarians are encouraged to use a face mask when dealing with infected animals. The use of vaccines on swine to prevent their infection is a major method of limiting swine to human transmission. Risk factors that may contribute to swine-to-human transmission

include smoking and, especially, not wearing gloves when working with sick animals—thereby increasing the likelihood of subsequent hand-to-eye, hand-to-nose or hand-to-mouth transmission.

Prevention of human to human transmission

Influenza spreads between humans when infected people cough or sneeze, then other people breathe in the virus or touch something with the virus on it and then touch their own face. "Avoid touching your eyes, nose or mouth. Germs spread this way." Swine flu cannot be spread by pork products, since the virus is not transmitted through food. The swine flu in humans is most contagious during the first five days of the illness although some people, most commonly children, can remain contagious for up to ten days. Diagnosis can be made by sending a specimen, collected during the first five days for analysis.



Thermal imaging camera & screen, photographed in an airport terminal in Greece. Thermal imaging can detect elevated body temperature, one of the signs of the virus H1N1 (Swine influenza).

Recommendations to prevent spread of the virus among humans include using standard infection control against influenza. This includes frequent washing of hands with soap and water or with alcohol-based hand sanitizers, especially after being out in public.

Chance of transmission is also reduced by disinfecting household surfaces, which can be done effectively with a diluted chlorine bleach solution.

Experts agree that hand-washing can help prevent viral infections, including ordinary influenza and the swine flu virus. Also not touching your eyes, nose or mouth with your hands helps to prevent the flu. Influenza can spread in coughs or sneezes, but an increasing body of evidence shows small droplets containing the virus can linger on tabletops, telephones and other surfaces and be transferred via the fingers to the eyes, nose or mouth. Alcohol-based gel or foam hand sanitizers work well to destroy viruses and bacteria. Anyone with flu-like symptoms such as a sudden fever, cough or muscle aches should stay away from work or public transportation and should contact a doctor for advice.

Social distancing is another tactic. It means staying away from other people who might be infected and can include avoiding large gatherings, spreading out a little at work, or perhaps staying home and lying low if an infection is spreading in a community. Public health and other responsible authorities have action plans which may request or require social distancing actions depending on the severity of the outbreak.

Vaccination

Vaccines are available for different kinds of swine flu. The U.S. Food and Drug Administration (FDA) approved the new swine flu vaccine for use in the United States on September 15, 2009. Studies by the National Institutes of Health (NIH), show that a single dose creates enough antibodies to protect against the virus within about 10 days.

Treatment

In swine

As swine influenza is rarely fatal to pigs, little treatment beyond rest and supportive care is required. Instead veterinary efforts are focused on preventing the spread of the virus throughout the farm, or to other farms. Vaccination and animal management techniques are most important in these efforts. Antibiotics are also used to treat this disease, which although they have no effect against the influenza virus, do help prevent bacterial pneumonia and other secondary infections in influenza-weakened herds.

In humans

If a person becomes sick with swine flu, antiviral drugs can make the illness milder and make the patient feel better faster. They may also prevent serious flu complications. For treatment, antiviral drugs work best if started soon after getting sick (within 2 days of symptoms). Beside antivirals, supportive care at home or in hospital, focuses on controlling fevers, relieving pain and maintaining fluid balance, as well as identifying and treating any secondary infections or other medical problems. The U.S. Centers for Disease Control and Prevention recommends the use of Tamiflu (oseltamivir) or Relenza

(zanamivir) for the treatment and/or prevention of infection with swine influenza viruses; however, the majority of people infected with the virus make a full recovery without requiring medical attention or antiviral drugs. The virus isolates in the 2009 outbreak have been found resistant to amantadine and rimantadine.

In the U.S., on April 27, 2009, the FDA issued Emergency Use Authorizations to make available Relenza and Tamiflu antiviral drugs to treat the swine influenza virus in cases for which they are currently unapproved. The agency issued these EUAs to allow treatment of patients younger than the current approval allows and to allow the widespread distribution of the drugs, including by non-licensed volunteers.

Chapter 2

Influenza a Virus Subtype H1N1

Influenza A (H1N1) virus is a subtype of influenza A virus and was the most common cause of human influenza (flu) in 2009. Some strains of H1N1 are endemic in humans and cause a small fraction of all influenza-like illness and a small fraction of all seasonal influenza. H1N1 strains caused a few percent of all human flu infections in 2004–2005. Other strains of H1N1 are endemic in pigs (swine influenza) and in birds (avian influenza).

In June 2009, the World Health Organization declared the new strain of swine-origin H1N1 as a pandemic. This strain is often called **swine flu** by the public media. This novel virus spread worldwide and had caused about 17,000 deaths by the start of 2010. On August 10, 2010, the World Health Organization declared the H1N1 influenza pandemic over, saying worldwide flu activity had returned to typical seasonal patterns.

Swine influenza

Swine influenza (also called swine flu, or pig flu) is an infection by any one of several types of swine influenza virus. Swine influenza virus (SIV) is any strain of the influenza family of viruses that is endemic in pigs. As of 2009, the known SIV strains include influenza C and the subtypes of influenza A known as H1N1, H1N2, H3N1, H3N2, and H2N3.

Swine influenza virus is common throughout pig populations worldwide. Transmission of the virus from pigs to humans is not common and does not always lead to human influenza, often resulting only in the production of antibodies in the blood. If transmission does cause human influenza, it is called zoonotic swine flu. People with regular exposure to pigs are at increased risk of swine flu infection. The meat of an infected animal poses no risk of infection when properly cooked.

Pigs experimentally infected with the strain of swine flu that is causing the current human pandemic showed clinical signs of flu within four days, and the virus spread to other uninfected pigs housed with the infected ones.

During the mid-20th century, identification of influenza subtypes became possible, allowing accurate diagnosis of transmission to humans. Since then, only 50 such

transmissions have been confirmed. These strains of swine flu rarely pass from human to human. Symptoms of zoonotic swine flu in humans are similar to those of influenza and of influenza-like illness in general, namely chills, fever, sore throat, muscle pains, severe headache, coughing, weakness and general discomfort. The recommended time of isolation is about five days.

Notable incidents

Spanish flu

The Spanish flu, also known as *la grippe*, *La Gripe Española*, or *La Pesadilla*, was an unusually severe and deadly strain of avian influenza, a viral infectious disease, that killed some 50 to 100 million people worldwide over about a year in 1918 and 1919. It is thought to be one of the most deadly pandemics in human history.

The 1918 flu caused an unusual number of deaths, possibly due to it causing a cytokine storm in the body. (The current H5N1 bird flu, also an Influenza A virus, has a similar effect.) The Spanish flu virus infected lung cells, leading to overstimulation of the immune system via release of cytokines into the lung tissue. This leads to extensive leukocyte migration towards the lungs, causing destruction of lung tissue and secretion of liquid into the organ. This makes it difficult for the patient to breathe. In contrast to other pandemics, which mostly kill the old and the very young, the 1918 pandemic killed unusual numbers of young adults, which may have been due to their healthy immune systems mounting a too-strong and damaging response to the infection.

The term "Spanish" flu was coined because Spain was at the time the only European country where the press were printing reports of the outbreak, which had killed thousands in the armies fighting World War I. Other countries suppressed the news in order to protect morale.

Fort Dix outbreak

In 1976, a novel swine influenza A (H1N1) caused severe respiratory illness in 13 soldiers with 1 death at Fort Dix, New Jersey. The virus was detected only from January 19 to February 9 and did not spread beyond Fort Dix.

Russian flu

The 1977–1978 Russian flu epidemic was caused by strain *Influenza A/USSR/90/77 (H1N1)*. It infected mostly children and young adults under 23 because a similar strain was prevalent in 1947–57, causing most adults to have substantial immunity. The virus was included in the 1978–1979 influenza vaccine.

2009 A(H1N1) pandemic

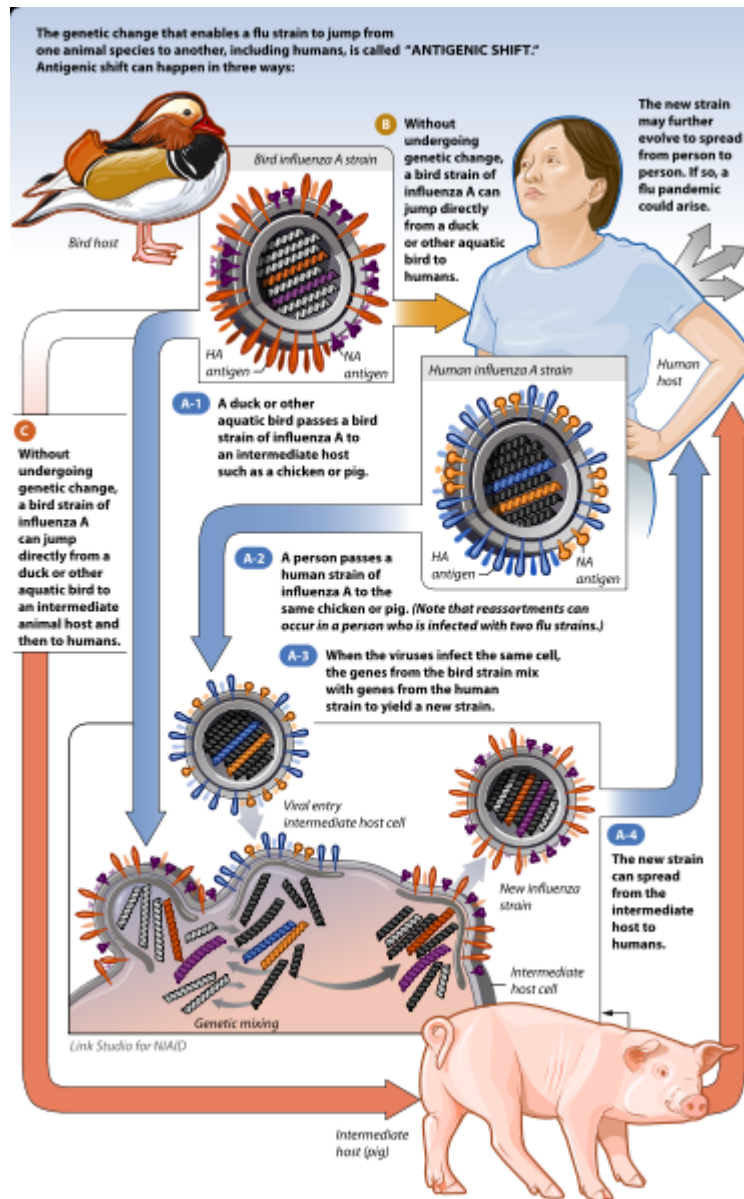


Illustration of influenza antigenic shift

In the 2009 flu pandemic, the virus isolated from patients in the United States was found to be made up of genetic elements from four different flu viruses – North American swine influenza, North American avian influenza, human influenza, and swine influenza virus typically found in Asia and Europe – "an unusually mongrelised mix of genetic sequences." This new strain appears to be a result of reassortment of human influenza and swine influenza viruses, in all four different strains of subtype H1N1.

Preliminary genetic characterization found that the hemagglutinin (HA) gene was similar to that of swine flu viruses present in U.S. pigs since 1999, but the neuraminidase (NA)

and matrix protein (M) genes resembled versions present in European swine flu isolates. The six genes from American swine flu are themselves mixtures of swine flu, bird flu, and human flu viruses. While viruses with this genetic makeup had not previously been found to be circulating in humans or pigs, there is no formal national surveillance system to determine what viruses are circulating in pigs in the U.S.

In April 2009, an outbreak of Influenza-like illness occurred in Mexico and the USA; the CDC reported seven cases of novel A/H1N1 influenza. By April 24 it became clear that the outbreak of ILI in Mexico and the confirmed cases of novel influenza A in the southwest US were related and WHO issued a health advisory on the outbreak of "influenza like illness in the United States and Mexico". The disease then spread very rapidly, with the number of confirmed cases rising to 2,099 by May 7, despite aggressive measures taken by the Mexican government to curb the spread of the disease.

On June 11, 2009, the WHO declared an H1N1 pandemic, moving the alert level to phase 6, marking the first global pandemic since the 1968 Hong Kong flu.

On October 25, 2009 U.S. President Barack Obama officially declared H1N1 a national emergency. Despite President Obama's concern, a Fairleigh Dickinson University PublicMind poll found in October 2009 that an overwhelming majority of New Jerseyans (74%) were not very worried or not at all worried about contracting the H1N1 flu virus.

A study conducted in coordination with the University of Michigan Health Service is scheduled for publication in the December 2009 *American Journal of Roentgenology* warning that H1N1 flu can cause pulmonary embolism, surmised as a leading cause of death in this current pandemic. The study authors suggest physician evaluation via contrast enhanced CT scans for the presence of pulmonary emboli when caring for patients diagnosed with respiratory complications from a "severe" case of the H1N1 flu.

March 21, 2010 worldwide update by the U.N.'s World Health Organization (WHO) states that "213 countries and overseas territories/communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 16,931 deaths."

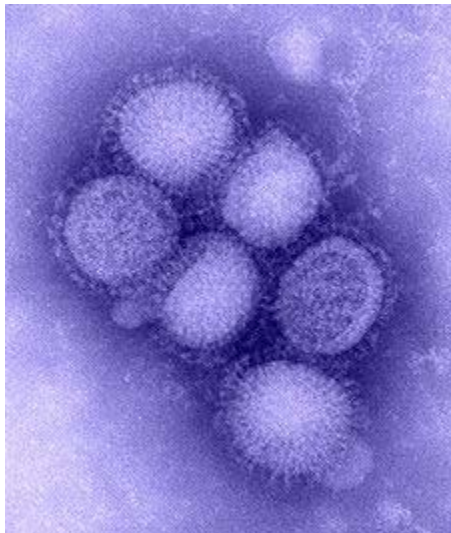
As of May 30, 2010 worldwide update by World Health Organization(WHO) more than 214 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18138 deaths.

The research team of Andrew Miller MD showed pregnant patients are at increased risk.

Chapter 3

2009 Flu Pandemic

Pandemic H1N1/09 Influenza



Electron microscope image of the reassorted H1N1 influenza virus. The viruses are ~100 nanometres in diameter.

MedlinePlus 007421

MeSH D053118

The **2009 flu pandemic** was an outbreak of a new strain of H1N1 influenza virus, usually referred to as "swine flu". First described in April 2009, the virus appeared to be a new strain of H1N1 which resulted when a previous triple reassortment of bird, bacon and human flu viruses further combined with a Eurasian pig flu virus. Unlike most strains of influenza, H1N1 does not disproportionately infect adults older than 60 years; this was an unusual and characteristic feature of the H1N1 pandemic. Even in the case of previously very healthy persons, a small percentage will develop pneumonia or acute respiratory distress syndrome. This manifests itself as increased breathing difficulty and typically

occurs 3–6 days after initial onset of flu symptoms. The pneumonia caused by flu can be either direct viral pneumonia or a secondary bacterial pneumonia. In fact, a November 2009 *New England Journal of Medicine* article recommends that flu patients whose chest X-ray indicates pneumonia receive both antivirals and antibiotics. In particular, it is a warning sign if a child (and presumably an adult) seems to be getting better and then relapses with high fever, as this relapse may be bacterial pneumonia.

The outbreak began in the state of Veracruz, Mexico, with evidence that there had been an ongoing epidemic for months before it was officially recognized as such. The Mexican government closed most of Mexico City's public and private facilities in an attempt to contain the spread of the virus; however, it continued to spread globally, and clinics in some areas were overwhelmed by infected people. In June, the World Health Organization (WHO) and US Centers for Disease Control (CDC) stopped counting cases and declared the outbreak a pandemic.

Despite being informally called "swine flu", the H1N1 flu virus cannot be spread by eating pork or pork products; similar to other influenza viruses, it is typically contracted by person to person transmission through respiratory droplets. Symptoms usually last 4–6 days. Antivirals (oseltamivir or zanamivir) were recommended for those with more severe symptoms or those in an at-risk group. Currently, there are 14,286 confirmed deaths worldwide. This figure is a sum of confirmed deaths reported by national authorities; the WHO states that total mortality (including deaths unconfirmed or unreported) from the new H1N1 strain is "unquestionably higher".

The pandemic began to taper off in November 2009, and by May 2010, the number of cases was in steep decline. On 10 August 2010, the Director-General of the World Health Organization, Margaret Chan, announced the end of the H1N1 pandemic. Chan noted that the H1N1 pandemic could have been much worse. According to the latest WHO statistics, the virus has killed more than 18,000 people since it appeared in April 2009, approximately 4% of the 250,000 to 500,000 annual influenza deaths. Research released in September 2010 disclosed that children with the pandemic flu were less likely to develop complications than those sick with seasonal flu strains, contradicting early reports on the severity of the pandemic. Critics claimed the WHO had exaggerated the danger, spreading "fear and confusion" rather than "immediate information". The WHO began an investigation to determine whether it had "frightened people unnecessarily".

Classification

The initial outbreak was called the "H1N1 influenza", or "Swine Flu" by American media. It is called pandemic H1N1/09 virus by the World Health Organization, while the U.S. Centers for Disease Control refer to it as "novel influenza A (H1N1)" or "2009 H1N1 flu". In the Netherlands, it was originally called "Pig Flu", but is now called "New Influenza A (H1N1)" by the national health institute, although the media and general population use the name "Mexican Flu". South Korea and Israel briefly considered calling it the "Mexican virus". Later, the South Korean press used "SI", short for "swine influenza". Taiwan suggested the names "H1N1 flu" or "new flu", which most local

media adopted. The World Organization for Animal Health proposed the name "North American influenza". The European Commission adopted the term "novel flu virus".

Signs and symptoms

The symptoms of H1N1 flu are similar to those of other influenzas, and may include a fever, cough (typically a "dry cough"), headache, muscle or joint pain, sore throat, chills, fatigue, and runny nose. Diarrhea, vomiting, and neurological problems have also been reported in some cases. People at higher risk of serious complications include those aged over 65, children younger than 5, children with neurodevelopmental conditions, pregnant women (especially during the third trimester), and those of any age with underlying medical conditions, such as asthma, diabetes, obesity, heart disease, or a weakened immune system (e.g., taking immunosuppressive medications or infected with HIV). More than 70% of hospitalizations in the U.S. have been people with such underlying conditions, according to the CDC.

In September 2009, the CDC reported that the H1N1 flu "seems to be taking a heavier toll among chronically ill children than the seasonal flu usually does." Through 8 August 2009, the CDC had received 36 reports of paediatric deaths with associated influenza symptoms and laboratory-confirmed pandemic H1N1 from state and local health authorities within the United States, with 22 of these children having neurodevelopmental conditions such as cerebral palsy, muscular dystrophy, or developmental delays. "Children with nerve and muscle problems may be at especially high risk for complications because they cannot cough hard enough to clear their airways". From 26 April 2009, to 13 February 2010, the CDC had received reports of the deaths of 277 children with laboratory-confirmed 2009 influenza A (H1N1) within the United States.

Symptoms in severe cases

The World Health Organization reports that the clinical picture in severe cases is strikingly different from the disease pattern seen during epidemics of seasonal influenza. While people with certain underlying medical conditions are known to be at increased risk, many severe cases occur in previously healthy people. In severe cases, patients generally begin to deteriorate around three to five days after symptom onset. Deterioration is rapid, with many patients progressing to respiratory failure within 24 hours, requiring immediate admission to an intensive care unit. Upon admission, most patients need immediate respiratory support with mechanical ventilation.

A November 2009 CDC recommendation stated that the following constitute "emergency warning signs" and advised seeking immediate care if a person experiences any one of these signs:

In adults:

- Difficulty breathing or shortness of breath
- Pain or pressure in the chest or abdomen

- Sudden dizziness
- Confusion
- Severe or persistent vomiting
- Low temperature

In children:

- Fast breathing or working hard to breathe
- Bluish skin color
- Not drinking enough fluids
- Not waking up or not interacting
- Being so irritable that the child does not want to be held
- Flu-like symptoms which improve but then return with fever and worse cough
- Fever with a rash
- Being unable to eat
- Having no tears when crying

Research later indicated that the severe flu effects in healthy young and middle-aged adults are caused by an excessive immune response.

Complications

Most complications have occurred among previously healthy individuals, with obesity and respiratory disease as the strongest risk factors. Pulmonary complications are common. Primary influenza pneumonia occurs most commonly in adults and may progress rapidly to acute lung injury requiring mechanical ventilation. Secondary bacterial infection is more common in children. *Staphylococcus aureus*, including methicillin-resistant strains, is an important cause of secondary bacterial pneumonia with a high mortality rate. Neuromuscular and cardiac complications are unusual but may occur.

A United Kingdom investigation of risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza looked at 631 patients from 55 hospitals admitted with confirmed infection from May through September 2009. 13% were admitted to a high dependency or intensive care unit and 5% died; 36% were aged <16 years and 5% were aged ≥ 65 years. Non-white and pregnant patients were over-represented. 45% of patients had at least one underlying condition, mainly asthma, and 13% received antiviral drugs before admission. Of 349 with documented chest x-rays on admission, 29% had evidence of pneumonia, but bacterial co-infection was uncommon. Multivariate analyses showed that physician-recorded obesity on admission and pulmonary conditions other than asthma or chronic obstructive pulmonary disease (COPD) were associated with a severe outcome, as were radiologically confirmed pneumonia and a raised C-reactive protein (CRP) level (≥ 100 mg/l). 59% of all in-hospital deaths occurred in previously healthy people.

Fulminant (sudden-onset) myocarditis has been linked to infection with H1N1, with at least four cases of myocarditis confirmed in patients also infected with A/H1N1. Three out of the four cases of H1N1-associated myocarditis were classified as fulminant, and one of the patients died. Also, there appears to be a link between severe A/H1N1 influenza infection and pulmonary embolism. In one report, five out of 14 patients admitted to the intensive care unit with severe A/H1N1 infection were found to have pulmonary emboli.

An article published in *JAMA* in September 2010 challenged previous reports and stated that children infected in the 2009 flu pandemic were no more likely to be hospitalised with complications or get pneumonia than those who catch seasonal strains. Researchers found that about 1.5 percent of children with the H1N1 swine flu strain were hospitalised within 30 days, compared with 3.7 percent of those sick with a seasonal strain of H1N1 and 3.1 percent with an H3N2 virus.

Diagnosis

Confirmed diagnosis of pandemic H1N1 flu requires testing of a nasopharyngeal, nasal or oropharyngeal tissue swab from the patient. Real-time RT-PCR is the recommended test as others are unable to differentiate between pandemic H1N1 and regular seasonal flu. However, most people with flu symptoms do not need a test for pandemic H1N1 flu specifically, because the test results usually do not affect the recommended course of treatment. The U.S. CDC recommend testing only for people who are hospitalised with suspected flu, pregnant women and people with weakened immune systems. For the mere diagnosis of influenza and not pandemic H1N1 flu specifically, more widely available tests include rapid influenza diagnostic tests (RIDT), which yield results in about 30 minutes, and direct and indirect immunofluorescence assays (DFA and IFA), which take 2–4 hours. Due to the high rate of RIDT false negatives, the CDC advise that patients with illnesses compatible with novel influenza A (H1N1) virus infection but with negative RIDT results should be treated empirically based on the level of clinical suspicion, underlying medical conditions, severity of illness and risk for complications, and if a more definitive determination of infection with influenza virus is required, testing with rRT-PCR or virus isolation should be performed. Dr. Rhonda Medows of the Georgia Department of Community Health states that the rapid tests are incorrect anywhere from 30 to 90% of the time and warns doctors in her state not to use them because they are wrong so often. The use of RIDTs has also been questioned by researcher Paul Schreckenberger of the Loyola University Health System, who suggests that rapid tests may actually pose a dangerous public health risk. Dr. Nikki Shindo of the WHO has expressed regret at reports of treatment being delayed by waiting for H1N1 test results and suggests, "[D]octors should not wait for the laboratory confirmation but make diagnosis based on clinical and epidemiological backgrounds and start treatment early".

On 22 June 2010, the CDC announced a new test called the "CDC Influenza 2009 A (H1N1)pdm Real-Time RT-PCR Panel (IVD)". It uses a molecular biology technique to detect influenza A viruses and specifically the 2009 H1N1 virus. The new test will replace the previous real-time RT-PCR diagnostic test used during the 2009 H1N1

pandemic, which received an emergency use authorisation from the U.S. Food and Drug Administration in April 2009. Tests results are available in four hours and are 96% accurate.

Virus characteristics

The virus was found to be a novel strain of influenza for which extant vaccines against seasonal flu provided little protection. A study at the U.S. Centers for Disease Control and Prevention published in May 2009 found that children had no preexisting immunity to the new strain but that adults, particularly those over 60, had some degree of immunity. Children showed no cross-reactive antibody reaction to the new strain, adults aged 18 to 64 had 6–9%, and older adults 33%. While it has been thought that these findings suggest the partial immunity in older adults may be due to previous exposure to similar seasonal influenza viruses, a November 2009 study of a rural unvaccinated population in China found only a 0.3% cross-reactive antibody reaction to the H1N1 strain, suggesting that previous vaccinations for seasonal flu and not exposure may have resulted in the immunity found in the older U.S. population.

It has been determined that the strain contains genes from five different flu viruses: North American swine influenza, North American avian influenza, human influenza and two swine influenza viruses typically found in Asia and Europe. Further analysis has shown that several proteins of the virus are most similar to strains that cause mild symptoms in humans, leading virologist Wendy Barclay to suggest on 1 May 2009 that the initial indications are that the virus was unlikely to cause severe symptoms for most people.

The virus is currently less lethal than previous pandemic strains and kills about 0.01–0.03% of those infected; the 1918 influenza was about one hundred times more lethal and had a case fatality rate of 2–3%. By 14 November 2009, the virus had infected one in six Americans with 200,000 hospitalisations and 10,000 deaths – as many hospitalizations and fewer deaths than in an average flu season overall, but with much higher risk for those under 50. With deaths of 1,100 children and 7,500 adults 18 to 64, these figures "are much higher than in a usual flu season".

In June 2010, scientists from Hong Kong reported discovery of a new swine flu virus which is a hybrid of the pandemic H1N1 virus and viruses previously found in pigs. It is the first report of a reassortment of the pandemic virus, which in humans has been slow to evolve. Nancy Cox, head of the influenza division at the U.S. Centers for Disease Control, has said, "This particular paper is extremely interesting because it demonstrates for the first time what we had worried about at the very onset of the pandemic, and that is that this particular virus, when introduced into pigs, could reassort with the resident viruses in pigs and we would have new gene constellations. And bingo, here we are." Pigs have been termed the mixing vessel of flu because they can be infected both by avian flu viruses, which rarely directly infect people, and by human viruses. When pigs become simultaneously infected with more than one virus, the viruses can swap genes, producing new variants which can pass to humans and sometimes spread amongst them. "Unlike the situation with birds and humans, we have a situation with pigs and humans

where there's a two-way street of exchange of viruses. With pigs it's very much a two-way street".

Transmission

Spread of the H1N1 virus is thought to occur in the same way that seasonal flu spreads. Flu viruses are spread mainly from person to person through coughing or sneezing by people with influenza. Sometimes people may become infected by touching something – such as a surface or object – with flu viruses on it and then touching their face. "Avoid touching your eyes, nose or mouth. Germs spread this way".

The basic reproduction number (the average number of other individuals whom each infected individual will infect, in a population which has no immunity to the disease) for the 2009 novel H1N1 is estimated to be 1.75. A December 2009 study found that the transmissibility of the H1N1 influenza virus in households is lower than that seen in past pandemics. Most transmissions occur soon before or after the onset of symptoms.

The H1N1 virus has been transmitted to animals, including swine, turkeys, ferrets, household cats, at least one dog and a cheetah.

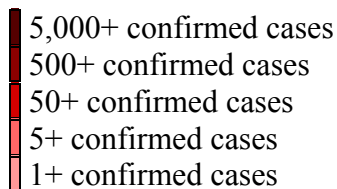
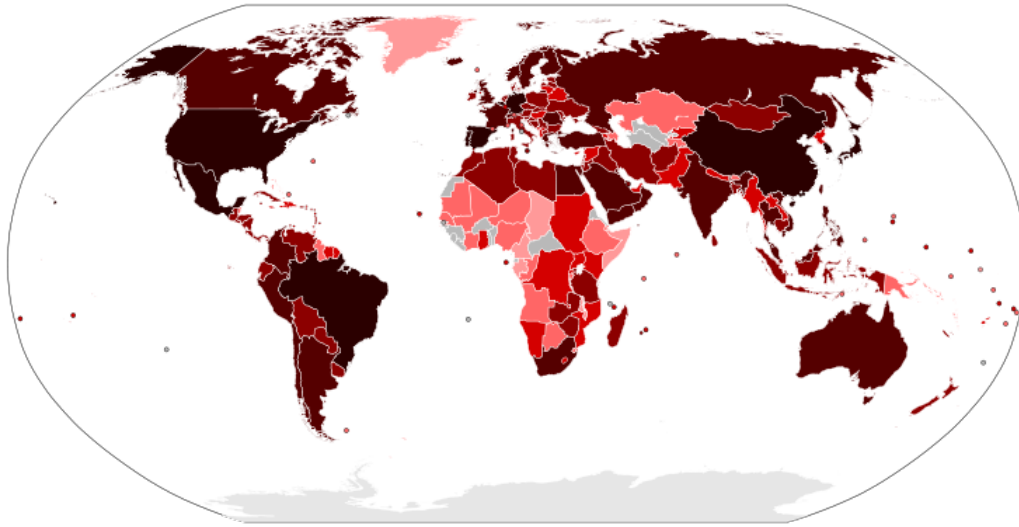
Prevention

The H1N1 vaccine was initially in short supply and in the U.S., the CDC recommended that initial doses should go to priority groups such as pregnant women, people who live with or care for babies under six months old, children six months to four years old and health-care workers. In the UK, the NHS recommended vaccine priority go to people over six months old who were clinically at risk for seasonal flu, pregnant women and households of people with compromised immunity.

Although it was initially thought that two injections would be required, clinical trials showed that the new vaccine protected adults "with only one dose instead of two", and so the limited vaccine supplies would go twice as far as had been predicted. Health officials worldwide were also concerned because the virus was new and could easily mutate and become more virulent, even though most flu symptoms were mild and lasted only a few days without treatment. Officials also urged communities, businesses and individuals to make contingency plans for possible school closures, multiple employee absences for illness, surges of patients in hospitals and other effects of potentially widespread outbreaks.

In February 2010, the CDC's Advisory Committee on Immunization Practices voted for "universal" flu vaccination in the U.S. to include all people over six months of age. The 2010-2011 vaccine will protect against the 2009 H1N1 pandemic virus and two other flu viruses.

Public health response



On 27 April 2009, the European Union health commissioner advised Europeans to postpone nonessential travel to the United States or Mexico. This followed the discovery of the first confirmed case in Spain. On 6 May 2009, the Public Health Agency of Canada announced that their National Microbiology Laboratory (NML) had mapped the genetic code of the swine flu virus, the first time that had been done. In the U.K., the National Health Service launched a website, the National Pandemic Flu Service, allowing patients to self-assess and get an authorisation number for antiviral medication. The system was expected to reduce the burden on general practitioners.

U.S. officials observed that six years of concern about H5N1 avian flu did much to prepare for the current H1N1 flu outbreak, noting that after H5N1 emerged in Asia, ultimately killing about 60% of the few hundred people infected by it over the years, many countries took steps to try to prevent any similar crisis from spreading further. The CDC and other American governmental agencies used the summer lull to take stock of the United States' response to H1N1 flu and attempt to patch any gaps in the public health safety net before flu season started in early autumn. Preparations included planning a second influenza vaccination program in addition to that for seasonal influenza, and improving coordination between federal, state and local governments and private health providers. On 24 October 2009, U.S. President Obama declared swine flu a national emergency, giving Secretary of Health and Human Services Kathleen Sebelius authority to grant waivers to requesting hospitals from usual federal requirements.

Vaccines



U.S. President Barack Obama being vaccinated against H1N1 flu on December 20, 2009, long after the pandemic had subsided in the U.S.

As of 19 November 2009, over 65 million doses of vaccine had been administered in over 16 countries; the vaccine seems safe and effective, producing a strong immune response that should protect against infection. Whereas the 2009 trivalent seasonal influenza vaccine neither increases nor decreases the risk of infection with H1N1, the vaccines rushed to combat the new strain are effective against H1N1, although they are manufactured similarly. Overall the safety profile of the new H1N1 vaccine is similar to that of the seasonal flu vaccine, and as of November 2009 fewer than a dozen cases of Guillain-Barre syndrome had been reported post-vaccination. Only a few of these were suspected to be actually related to the H1N1 vaccination, and only temporary illness had been observed. This is in strong contrast to the 1976 swine flu outbreak, when mass vaccinations in the United States caused over 500 cases of Guillain-Barre syndrome and led to 25 deaths. Although the vaccines were effective, many industrialised nations were giving away, selling, canceling orders for and destroying excess doses of the vaccine.

There are safety concerns for people who are allergic to eggs because the viruses for the vaccine are grown in chicken-egg-based cultures. People with egg allergies may be able to receive the vaccine, after consultation with their physician, in graded doses in a careful and controlled environment. A vaccine manufactured by Baxter is made without using eggs, but requires two doses three weeks apart to produce immunity.

As of late November 2009, in Canada there had been 24 confirmed cases of anaphylactic shock following vaccination, including one death. The estimated rate is one anaphylactic reaction per 312,000 persons receiving the vaccine; however, six persons had suffered anaphylaxis out of 157,000 doses given from one batch of vaccine. Dr. David Butler-Jones, Canada's chief public health officer, stated that even though this was an adjuvanted vaccine, that did not appear to be the cause of this severe allergic reaction in these six patients.

Accusations of conflict of interest

In January 2010, Wolfgang Wodarg, a German Social Democrat deputy who trained as a doctor and now chairs the health committee at the Council of Europe, claimed major firms had organised a "campaign of panic" to put pressure on the World Health Organisation (WHO) to declare a "false pandemic" to sell vaccines. Dr. Wodarg said the WHO's "false pandemic" flu campaign is "one of the greatest medicine scandals of the century". He said that the "false pandemic" campaign began last May in Mexico City, when a hundred or so "normal" reported influenza cases were declared to be the beginning of a threatening new pandemic, although he said there was little scientific evidence for this. Nevertheless he argued that the WHO, "in cooperation with some big pharmaceutical companies and their scientists, re-defined pandemics", removing the statement that "an enormous amount of people have contracted the illness or died" from its existing definition and replacing it by stating simply that there has to be a virus, spreading beyond borders and to which people have no immunity. The WHO responded by stating that they take their duty to provide independent advice seriously and guarded against interference from outside interests. Announcing a review of the WHO's actions, spokeswoman Fadela Chaib stated: "Criticism is part of an outbreak cycle. We expect and indeed welcome criticism and the chance to discuss it". In March 2010, the Council of Europe launched an enquiry into 'the influence of the pharmaceutical companies on the global swine flu campaign', and a preliminary report is in preparation.

On April 12, 2010, Keiji Fukuda, the WHO's top influenza expert, stated that the system leading to the declaration of a pandemic led to confusion about H1N1 circulating around the world, and he expressed concern that there was a failure to communicate in regard to uncertainties about the new virus, which turned out to be not as deadly as feared. WHO Director-General Margaret Chan has appointed 29 flu experts from outside the organization to conduct a review of WHO's handling of the H1N1 flu pandemic. She has told them, "We want a frank, critical, transparent, credible and independent review of our performance".

In June 2010, Fiona Godlee, editor in chief of the British medical journal *BMJ*, published an editorial which criticised the WHO, saying that an investigation had disclosed that some of the experts advising WHO on the pandemic had financial ties with drug companies which were producing antivirals and vaccines. Margaret Chan, Director-General of the WHO, replied stating, "Without question, the *BMJ* feature and editorial will leave many readers with the impression that WHO's decision to declare a pandemic was at least partially influenced by a desire to boost the profits of the pharmaceutical

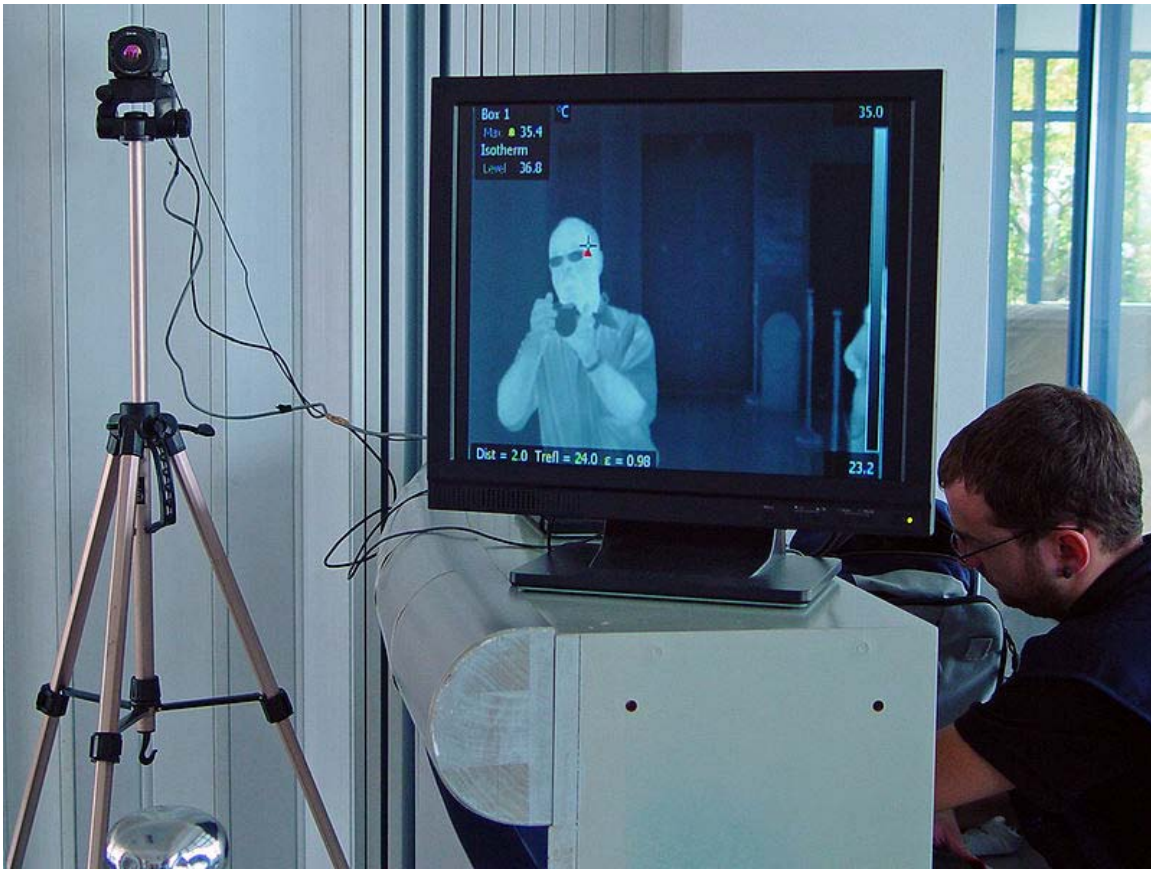
industry. The bottom line, however, is that decisions to raise the level of pandemic alert were based on clearly defined virological and epidemiological criteria. It is hard to bend these criteria, no matter what the motive". In August 2010, the *Daily Mail* printed an article stating that "a third of the experts advising the World Health Organisation about the swine flu pandemic had ties to drugs firms" and that of the 20 members of the Scientific Advisory Group for Emergencies, which advised the British Government on swine flu, 11 had done work for the pharmaceutical industry or were linked to it through their universities.

Infection control

Travel precautions



Flu inspection on a flight arriving in China



Thermal imaging camera and screen, photographed in an airport terminal in Greece. Thermal imaging can detect elevated body temperature, one of the signs of swine flu.

On 7 May 2009, the WHO stated that containment was not feasible and that countries should focus on mitigating the effect of the virus. They did not recommend closing borders or restricting travel. On 26 April 2009, the Chinese government announced that visitors returning from flu-affected areas who experienced flu-like symptoms within two weeks would be quarantined.

U.S. airlines had made no major changes as of the beginning of June 2009, but continued standing practices which include looking for passengers with symptoms of flu, measles or other infections, and relying on in-flight air filters to ensure that aircraft were sanitised. Masks were not generally provided by airlines and the CDC did not recommend that airline crews wear them. Some non-U.S. airlines, mostly Asian, including Singapore Airlines, China Eastern Airlines, China Southern Airlines, Cathay Pacific and Mexicana Airlines, took measures such as stepping up cabin cleaning, installing state-of-the-art air filters and allowing in-flight staff to wear face masks.

Schools

U.S. government officials have been especially concerned about schools because the H1N1 flu virus appears to disproportionately affect young and school-age people,

between six months and 24 years of age. The H1N1 outbreak led to numerous precautionary school closures in some areas. Rather than closing schools, the CDC recommended that students and school workers with flu symptoms should stay home for either seven days total, or until 24 hours after symptoms subsided, whichever was longer. The CDC also recommended that colleges should consider suspending fall 2009 classes if the virus began to cause severe illness in a significantly larger share of students than the previous spring. They also urged schools to suspend rules, such as penalties for late papers or missed classes or requirements for a doctor's note, to enforce "self-isolation" and prevent students from venturing out while ill; schools were advised to set aside a room for people developing flu-like symptoms while they waited to go home and to have ill students or staff and those caring for them use face masks.

In California, school districts and universities were on alert and working with health officials to launch education campaigns. Many planned to stockpile medical supplies and discuss worst-case scenarios, including plans to provide lessons and meals for low-income children in case elementary and secondary schools closed. University of California campuses stockpiled supplies, from paper masks and hand sanitizer to food and water. To help prepare for contingencies, University of Maryland School of Medicine professor of pediatrics James C. King Jr. suggested that every county should create an "influenza action team" to be run by the local health department, parents and school administrators. As of 28 October 2009, about 600 schools in the United States had been temporarily closed, affecting over 126,000 students in 19 states.

Workplace

Fearing a worst-case scenario, the U.S. Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention and the Department of Homeland Security (DHS) developed updated guidance and a video for employers to use as they developed plans to respond to the H1N1 outbreak. The guidance suggested that employers consider and communicate their objectives, such as reducing transmission among staff, protecting people who are at increased risk of influenza-related complications from becoming infected, maintaining business operations, and minimising adverse effects on other entities in their supply chains.

The CDC estimated that as much as 40% of the workforce might be unable to work at the peak of the pandemic due to the need for many healthy adults to stay home and care for an ill family member, and advised that individuals should have steps in place should a workplace close down or a situation arise that requires working from home. The CDC further advised that persons in the workplace should stay home sick for seven days after getting the flu, or 24 hours after symptoms end, whichever is longer.

In the UK, the Health and Safety Executive (HSE) also issued general guidance for employers.

Facial masks



Mexico City Metro

The U.S. CDC does not recommend use of face masks or respirators in non-health care settings, such as schools, workplaces, or public places, with a few exceptions: people who are ill with the virus when around other people, and people who are at risk for severe illness while caring for someone with the flu. There has been some disagreement about the value of wearing facial masks, some experts fearing that masks may give people a false sense of security and should not replace other standard precautions. Masks may benefit people in close contact with infected persons, but it is unknown whether they prevent H1N1 flu infection. Yukihiro Nishiyama, professor of virology at Nagoya University's School of Medicine, commented that the masks are "better than nothing, but it's hard to completely block out an airborne virus since it can easily slip through the gaps".

According to mask manufacturer 3M, masks will filter out particles in industrial settings, but "there are no established exposure limits for biological agents such as swine flu virus". However, despite the lack of evidence of effectiveness, the use of such masks is common in Asia. They are particularly popular in Japan, where cleanliness and hygiene are highly valued and where etiquette obligates those who are sick to wear masks to avoid spreading disease.

Quarantine

During the height of the fear of a pandemic, some countries initiated or threatened to initiate quarantines of foreign visitors suspected of having or being in contact with others who may have been infected. In May 2009, the Chinese government confined 21 U.S. students and three teachers to their hotel rooms. As a result, the US State Department issued a travel alert about China's anti-flu measures and warned travellers against travelling to China if ill. In Hong Kong, an entire hotel was quarantined with 240 guests; Australia ordered a cruise ship with 2,000 passengers to stay at sea because of a swine flu threat. Egyptian Muslims who went on the annual pilgrimage to Mecca risked being quarantined upon their return. Russia and Taiwan said they would quarantine visitors with fevers who come from areas where the flu was present. Japan quarantined 47 airline passengers in a hotel for a week in mid-May, then in mid-June India suggested pre-screening "outbound" passengers from countries thought to have a high rate of infection.

Pigs and food safety

The pandemic virus is a type of swine influenza, derived originally from a strain which lived in pigs, and this origin gave rise to the common name of "swine flu". This term is widely used by mass media. The virus has been found in American hogs, and Canadian as well as in hogs in Northern Ireland, Argentina, and Norway. Leading health agencies and the United States Secretary of Agriculture have stressed that eating properly cooked pork or other food products derived from pigs will not cause flu. Nevertheless, on April 27, Azerbaijan imposed a ban on the importation of animal husbandry products from America. The Indonesian government also halted the importation of pigs and initiated the examination of 9 million pigs in Indonesia. The Egyptian government ordered the slaughter of all pigs in Egypt on April 29, 2009.

Treatment

A number of methods have been recommended to help ease symptoms, including adequate liquid intake and rest. Over-the-counter pain medications such as acetaminophen and ibuprofen do not kill the virus; however, they may be useful to reduce symptoms. Aspirin and other salicylate products should not be used by people under 19 with any flu-type symptoms because of the risk of developing Reye's Syndrome.

If the fever is mild and there are no other complications, fever medication is not recommended. Most people recover without medical attention, although those with pre-existing or underlying medical conditions are more prone to complications and may benefit from further treatments.

People in at-risk groups should be treated with antivirals (oseltamivir or zanamivir) as soon as possible when they first experience flu symptoms. The at-risk groups include pregnant and post partum women, children under two years old, and people with underlying conditions such as respiratory problems. People who are not in an at-risk group who have persistent or rapidly worsening symptoms should also be treated with

antivirals. People who have developed pneumonia should be given both antivirals and antibiotics, as in many severe cases of H1N1-caused illness, bacterial infection develops. Antivirals are most useful if given within 48 hours of the start of symptoms and may improve outcomes in hospitalised patients. In those beyond 48 hours who are moderately or severely ill, antivirals may still be beneficial. If oseltamivir (Tamiflu) is unavailable or cannot be used, zanamivir (Relenza) is recommended as a substitute. Peramivir is an experimental antiviral drug approved for hospitalised patients in cases where the other available methods of treatment are ineffective or unavailable.

To help avoid shortages of these drugs, the U.S. CDC recommended oseltamivir treatment primarily for people hospitalised with pandemic flu; people at risk of serious flu complications due to underlying medical conditions; and patients at risk of serious flu complications. The CDC warned that the indiscriminate use of antiviral medications to prevent and treat influenza could ease the way for drug-resistant strains to emerge, which would make the fight against the pandemic that much harder. In addition, a British report found that people often failed to complete a full course of the drug or took the medication when not needed.

Side effects

Both medications have known side effects, including lightheadedness, chills, nausea, vomiting, loss of appetite and trouble breathing. Children were reported to be at increased risk of self-injury and confusion after taking oseltamivir. The WHO warn against buying antiviral medications from online sources, and estimate that half the drugs sold by online pharmacies without a physical address are counterfeit.

Resistance

As of December 2010, the World Health Organization (WHO) reported 314 samples of the 2009 pandemic H1N1 flu tested worldwide have shown resistance to oseltamivir (Tamiflu). This is not totally unexpected as 99.6% of the seasonal H1N1 flu strains tested have developed resistance to oseltamivir. No circulating flu has yet shown any resistance to zanamivir (Relenza), the other available anti-viral.

Effectiveness of antivirals questioned

On 8 December 2009, the Cochrane Collaboration, which reviews medical evidence, announced in a review published in *BMJ* that it had reversed its previous findings that the antiviral drugs oseltamivir (Tamiflu) and zanamivir (Relenza) can ward off pneumonia and other serious conditions linked to influenza. They reported that an analysis of 20 studies showed oseltamivir offered mild benefits for healthy adults if taken within 24 hours of onset of symptoms, but found no clear evidence it prevented lower respiratory tract infections or other complications of influenza. Their published finding relates only to its use in healthy adults with influenza; they say nothing about its use in patients judged to be at high risk of complications (pregnant women, children under five and those with underlying medical conditions), and uncertainty over its role in reducing

complications in healthy adults may still leave it as a useful drug for reducing the duration of symptoms. The drugs might eventually be demonstrated to be effective against flu-related complications; in general, the Cochrane Collaboration concluded "Paucity of good data".

Some specific results from the *BMJ* article include: "The efficacy of oral oseltamivir against symptomatic laboratory confirmed influenza was 61% (risk ratio 0.39, 95% confidence interval 0.18 to 0.85) at 75 mg daily ... The remaining evidence suggests oseltamivir did not reduce influenza related lower respiratory tract complications (risk ratio 0.55, 95% confidence interval 0.22 to 1.35)". Notice especially the wide range for this second result.

Epidemiology

2009 flu pandemic data	
Area	Confirmed deaths
Worldwide (total)	14,286
European Union and EFTA	2,290
Other European countries and Central Asia	457
Mediterranean and Middle East	1,450
Africa	116
North America	3,642
Central America and Caribbean	237
South America	3,190
Northeast Asia and South Asia	2,294
Southeast Asia	393
Australia and Pacific	217

While it is not known precisely where or when the virus originated, analyses in scientific journals have suggested that the H1N1 strain responsible for the current outbreak first evolved in September 2008 and circulated amongst humans for several months before being formally recognised and identified as a novel strain of influenza.

Mexico

The virus was first reported in two U.S. children in March 2009, but health officials have reported that it apparently infected people as early as January 2009 in Mexico. The outbreak was first detected in Mexico City on 18 March 2009; immediately after the outbreak was officially announced, Mexico notified the U.S. and World Health Organization, and within days of the outbreak Mexico City was "effectively shut down". Some countries cancelled flights to Mexico while others halted trade. Calls to close the border to contain the spread were rejected. Mexico already had hundreds of non-lethal cases before the outbreak was officially discovered, and was therefore in the midst of a "silent epidemic". As a result, Mexico was reporting only the most serious cases which showed more severe signs different from those of normal flu, possibly leading to a skewed initial estimate of the case fatality rate.

United States

The new strain was first identified by the CDC in two children, neither of whom had been in contact with pigs. The first case, from San Diego County, California, was confirmed from clinical specimens (nasopharyngeal swab) examined by the CDC on 14 April 2009. A second case, from nearby Imperial County, California, was confirmed on 17 April. The patient in the first confirmed case had flu symptoms including fever and cough on clinical examination on 30 March, and the second on 28 March.

The first confirmed H1N1/09 pandemic flu death, which occurred at Texas Children's Hospital in Houston, Texas, was of a toddler from Mexico City who was visiting family in Brownsville, Texas, before being air-lifted to Houston for treatment.

Data reporting and accuracy

Influenza surveillance information "answers the questions of where, when, and what influenza viruses are circulating. It can be used to determine if influenza activity is increasing or decreasing, but cannot be used to ascertain how many people have become ill with influenza". For example, as of late June 2009, influenza surveillance information showed the U.S. had nearly 28,000 laboratory-confirmed cases including 3,065 hospitalisations and 127 deaths; but mathematical modelling showed an estimated 1 million Americans currently had the 2009 pandemic flu, according to Lyn Finelli, a flu surveillance official with the CDC. Estimating deaths from influenza is also a complicated process. In 2005, influenza only appeared on the death certificates of 1,812 people in the US. The average annual US death toll from flu is, however, estimated to be 36,000. The CDC explains: "[I]nfluenza is infrequently listed on death certificates of people who die from flu-related complications" and hence, "Only counting deaths where influenza was included on a death certificate would be a gross underestimation of influenza's true impact".

With respect to the current H1N1 flu pandemic, influenza surveillance information is available but almost no studies have attempted to estimate the total number of deaths

attributable to H1N1 flu. Two studies have been performed by the CDC, however; the most recent estimates that there were 9,820 deaths (range 7,070–13,930) attributable to H1N1 flu from April to 14 November 2009. During the same period, 1642 deaths were officially confirmed as caused by H1N1 flu. The WHO state that total mortality (including deaths unconfirmed or unreported) from H1N1 flu is "unquestionably higher" than their own confirmed death statistics.

The initial outbreak received a week of near-constant media attention. Epidemiologists cautioned that the number of cases reported in the early days of an outbreak can be very inaccurate and deceptive due to several causes, among them selection bias, media bias and incorrect reporting by governments. Inaccuracies could also be caused by authorities in different countries looking at differing population groups. Furthermore, countries with poor health care systems and older laboratory facilities may take longer to identify or report cases. "[E]ven in developed countries the [numbers of flu deaths] are uncertain, because medical authorities don't usually verify who actually died of influenza and who died of a flu-like illness". Dr. Joseph S. Bresee (the CDC flu division's epidemiology chief) and Dr. Michael T. Osterholm (director of the Center for Infectious Disease Research) have pointed out that millions of people have had H1N1 flu, usually in a mild form, so the numbers of laboratory-confirmed cases were actually meaningless, and in July 2009 the WHO stopped keeping count of individual cases and focused more on major outbreaks.

History of influenza epidemics

Annual influenza epidemics are estimated to affect 5–15% of the global population. Although most cases are mild, these epidemics still cause severe illness in 3–5 million people and 250,000–500,000 deaths worldwide. On average 41,400 people die of influenza each year in the United States, based on data collected between 1979 and 2001. In industrialised countries, severe illness and deaths occur mainly in the high-risk populations of infants, the elderly and chronically ill patients, although the H1N1 flu outbreak (like the 1918 Spanish flu) differs in its tendency to affect younger, healthier people.

In addition to these annual epidemics, Influenza A virus strains caused three global pandemics during the 20th century: the Spanish flu in 1918, Asian flu in 1957, and Hong Kong flu in 1968–69. These virus strains had undergone major genetic changes for which the population did not possess significant immunity. Recent genetic analysis has revealed that three-quarters, or six out of the eight genetic segments, of the 2009 flu pandemic strain arose from the North American swine flu strains circulating since 1998, when a new strain was first identified on a factory farm in North Carolina, and which was the first-ever reported triple-hybrid flu virus.

The 1918 flu epidemic began with a wave of mild cases in the spring, followed by more deadly waves in the autumn, eventually killing hundreds of thousands in the United States. The great majority of deaths in the 1918 flu pandemic were the result of secondary bacterial pneumonia. The influenza virus damaged the lining of the bronchial tubes and

lungs of victims, allowing common bacteria from the nose and throat to infect their lungs. Subsequent pandemics have had many fewer fatalities due to the development of antibiotic medicines which can treat pneumonia.

20th century flu pandemics

Pandemic	Year	Influenza virus type	People infected (approximate)	Estimated deaths worldwide	Case fatality rate
Spanish flu	1918–1919	A/H1N1	33% (500 million)	20–100 million	>2.5%
Asian flu	1956–1958	A/H2N2	?	2 million	<0.1%
Hong Kong flu	1968–1969	A/H3N2	?	1 million	<0.1%
Seasonal flu	Every year	mainly A/H3N2, A/H1N1, and B	5–15% (340 million – 1 billion)	250,000–500,000 per year 14,286 (lab-confirmed;	<0.1%
Swine flu	2009–2010	Pandemic H1N1/09	> 622,482 (lab-confirmed)	ECDC) ≥8,768 (lab-confirmed; WHO)	0.03%

The influenza virus has also caused several pandemic threats over the past century, including the pseudo-pandemic of 1947 (thought of as mild because although globally distributed, it caused relatively few deaths), the 1976 swine flu outbreak and the 1977 Russian flu, all caused by the H1N1 subtype. The world has been at an increased level of alert since the SARS epidemic in Southeast Asia (caused by the SARS coronavirus). The level of preparedness was further increased and sustained with the advent of the H5N1 bird flu outbreaks because of H5N1's high fatality rate, although the strains currently prevalent have limited human-to-human transmission (anthroponotic) capability, or epidemicity.

People who contracted flu before 1957 appeared to have some immunity to H1N1 flu. Dr. Daniel Jernigan, head of flu epidemiology for the the U.S. CDC, has stated: "Tests on blood serum from older people showed that they had antibodies that attacked the new virus ... That does not mean that everyone over 52 is immune, since Americans and Mexicans older than that have died of the new flu".

Chapter 4

Pandemic H1N1/09 Virus

The **Pandemic H1N1/09 virus** is a swine origin Influenza A virus subtype H1N1 virus strain responsible for the 2009 flu pandemic.

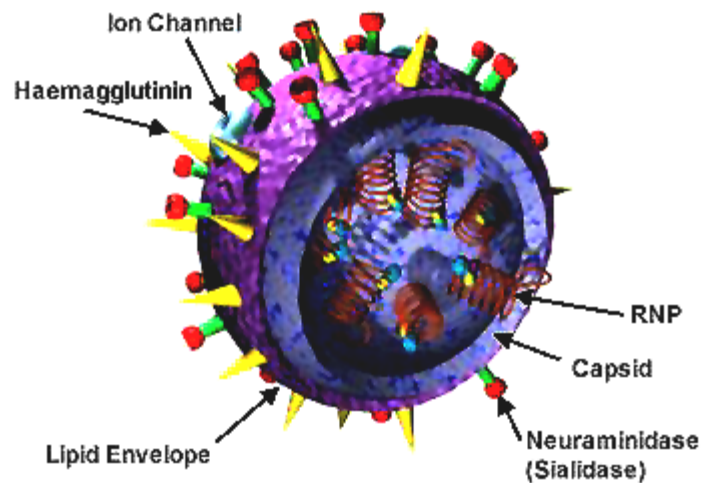
Virus characteristics

The virus is a novel strain of influenza. Existing vaccines against seasonal flu provide no protection. A study at the U.S. Centers for Disease Control and Prevention (CDC) published in May 2009 found that children had no preexisting immunity to the new strain but that adults, particularly those over 60, had some degree of immunity. Children showed no cross-reactive antibody reaction to the new strain, adults aged 18 to 64 had 6-9%, and older adults 33%. Much reporting of early analysis repeated that the strain contained genes from five different flu viruses: North American swine influenza, North American avian influenza, human influenza, and two swine influenza viruses typically found in Asia and Europe. Further analysis showed that several of the proteins of the virus are most similar to strains that cause mild symptoms in humans, leading virologist Wendy Barclay to suggest on May 1, 2009 that the initial indications are that the virus was unlikely to cause severe symptoms for most people. Other leading researchers indicated that all segments of the virus were in fact swine in origin, despite it being a multiple reassortment. The first complete genome sequence of the pandemic strain was deposited in public databases on April 27, 2009, by scientists from the U.S. Centers for Disease Control and Prevention in Atlanta. Scientists in Winnipeg later completed the full genetic sequencing of viruses from Mexico and Canada on May 6, 2009.

Virus origins

On June 23, 2009 *The New York Times* reported that U.S. federal agriculture officials, "contrary to the popular assumption that the new swine flu pandemic arose on factory farms in Mexico," now believe that it "most likely emerged in pigs in Asia, but then traveled to North America in a human." They emphasized that there was no way to prove their hypothesis, but stated that there is no evidence that this new virus, which combines Eurasian and North American genes, has ever circulated in North American pigs, "while there is tantalizing evidence that a closely related 'sister virus' has circulated in Asia."

In early June 2009, using computational methods developed over the last ten years, an international team of researchers attempted to reconstruct the origins and timescale of the 2009 flu pandemic. Dr Oliver Pybus of Oxford University's Department of Zoology, and part of the research team, claims "Our results show that this strain has been circulating among pigs, possibly among multiple continents, for many years prior to its transmission to humans." The research team that worked on this report also believe that it was "derived from several viruses circulating in swine," and that the initial transmission to humans occurred several months before recognition of the outbreak. The team concluded that "despite widespread influenza surveillance in humans, the lack of systematic swine surveillance allowed for the undetected persistence and evolution of this potentially pandemic strain for many years."



Structure of the influenza virion. The hemagglutinin (HA) and neuraminidase (NA) proteins are shown on the surface of the particle. The viral RNAs that make up the genome are shown as red coils inside the particle and bound to ribonucleoproteins (RNPs).

According to the researchers, movement of live pigs between Eurasia and North America "seems to have facilitated the mixing of diverse swine influenza viruses, leading to the multiple reassortment events associated with the genesis of the (new H1N1) strain." They also stated that this new pandemic "provides further evidence of the role of domestic pigs in the ecosystem of influenza A."

In November, 2009 a study was published in *Virology Journal* in which it was suggested that the virus may be the product of three strains from three continents that swapped genes in a lab or a vaccine-making plant, and subsequently "escaped". The study, published in a free, online journal reviewed by other scientists, follows debate among researchers in May, 2009, when the authors asked the World Health Organization to consider the hypothesis. After reviewing the initial paper, WHO and other organizations concluded the pandemic strain was a naturally occurring virus and not laboratory-derived.

Contagiousness

The virus is contagious and is believed to spread from human to human in much the same way as seasonal flu. The most common mechanisms by which it spreads are by droplets from coughs and sneezes of infected people, and also potentially touching a surface or the hand of a person contaminated with the virus and then touching one's eyes, nose or mouth, although there is no direct evidence for this. H1N1/09 is more contagious than seasonal flu, and infected people are contagious for longer than had been thought. The US CDC had recommended that people should wait at least a day after their fever subsides (usually 3–4 days after the onset of symptoms) before resuming normal activities, but it has been found that they can continue to shed virus for several days after that.

The contagiousness of the virus may change as it mutates.

Virulence

The virulence of swine flu virus is mild and the mortality rates are very low.

In mid-2009 the US Centers for Disease Control and Prevention (CDC) noted that most infections were mild, similar to seasonal flu, and that recovery tended to be fairly quick. The number of deaths as of September 2009 is sometimes misleadingly said to be a tiny fraction of the annual number of deaths from seasonal flu, but comparisons of human fatality figures with seasonal influenza are prone to underestimate impact of the pandemic and the pandemic H1N1/09 virus was in fact the dominant strain of influenza causing illness in the 2009/10 flu season.

Research carried out at Imperial College London has shown that, unlike seasonal flu, H1N1/09 can infect cells deep in the lungs. Seasonal flu can only infect cells with receptor type a2-6 which are typically located in the nose and throat but H1N1/09 can also infect cells with receptor type a2-3. This may explain why some patients experience severe respiratory symptoms. (The H5N1 virus is also able to infect cells deep in the lungs with receptor type a2-3 but cannot infect cells with receptor type a2-6 making it less contagious than H1N1/09.)

As of September 2009 most people infected by this flu suffer a mild illness, but the small minority hospitalized are often severely ill. Arand Kumar, intensive care expert at the University of Manitoba, Winnipeg, Canada, said "this pandemic is like two diseases; either you're off work for a few days or you go to hospital, often to the intensive-care unit (ICU). There's no middle ground." In the southern hemisphere 15 to 33% of hospitalized cases went to the ICU in July and August 2009. Unlike H5N1 avian flu and SARS which provoke a runaway body-wide immune response, H1N1/09 destroys the lungs' alveoli, often causing acute respiratory distress syndrome, which kills in half of all cases.

Preliminary research suggests that severity is linked to a genetic variation in immune systems.

From April 2009 to November 2009, in the US, 3,900 people have died of the H1N1 pandemic virus, sometimes compared to 36,000 people per year die from the "common flu", mostly in winter, although the former figure is for confirmed cases, whereas the latter is an estimate. The death rate of H1N1 in the US could be calculated as less than 0.02% from November 2009 figures from the CDC, and has been explicitly calculated as 0.026% in England.

Vaccine



2,500 people line up in a mall in Texas City, Texas to receive the H1N1 vaccine from the Galveston County Health Department.

Existing vaccines against seasonal flu provide no protection. Vaccines were released in North America in late October. Production may be 3 billion doses per year rather than the earlier estimate of 5 billion.

Evolutionary potential

On May 22, 2009, World Health Organization (WHO) Director-General Dr. Margaret Chan said that the virus must be closely monitored in the southern hemisphere, as it could mix with ordinary seasonal influenza and change in unpredictable ways. Experts writing in the July issue of *The New England Journal of Medicine* note that historically, pandemic viruses have evolved between seasons, and the current strain may become more severe or transmissible in the coming months. They therefore stress the importance

of international cooperation to engage in proper surveillance to help monitor changes in the virus's behavior, which will aid in both "vaccine targeting" and interpreting illness patterns in the fall of 2009.

Other experts are also concerned that the new virus strain could mutate over the coming months. Guan Yi, a leading virologist from the University of Hong Kong, for instance, described the new H1N1 influenza virus as "very unstable", meaning it could mix and swap genetic material (reassortment) when exposed to other viruses. During an interview he said "Both H1N1 and H5N1 are unstable so the chances of them exchanging genetic material are higher, whereas a stable (seasonal flu) virus is less likely to take on genetic material." The H5N1 virus is mostly limited to birds, but in rare cases when it infects humans it has a mortality rate of between 60% to 70%. Experts worry about the emergence of a hybrid of the more virulent Asian-lineage HPAI (highly pathogenic avian influenza) A/H5N1 strain (media labeled "bird flu") with more human-transmissible Influenza A strains such as this novel 2009 swine-origin A/H1N1 strain (media labeled "swine flu"), especially since the H5N1 strain is endemic among birds in countries like China, Indonesia, Vietnam and Egypt.

Other studies conclude that the virus is likely well adapted to humans, has a clear biological advantage over seasonal flu strains and that reassortment is unlikely at this time due to its current ease in replication and transmission.

However, Federal health officials in the U.S. noted that the horrific 1918 flu epidemic, which killed hundreds of thousands in the United States alone, was preceded by a mild "herald" wave of cases in the spring, followed by devastating waves of illness in the autumn.

As of late July 2009, U.S. health officials said that the swine flu isn't yet mutating to become more dangerous, but they are closely tracking that as the virus continues to circle the globe.

As of October 2009, research done by Taubenberger showed that the evolution of A (H1N1) is relatively slow since the structure of the 2009 H1N1 virus is similar to the strain of H1N1 implicated in the 1918 flu pandemic. A study from Hokkaido University found a homology between the Hemagglutinin antigen amino acid residues found in the earlier 1918 strain and the 2009 H1N1 strain. This may have played a role in individuals who had been infected with the 1918 strain and its early descendants in showing stronger specific immunity to the 2009 H1N1 virus. This finding provides insight into future monitoring of the H1N1 virus and its evolution within the human population.

Mutation

On November 20, 2009 the Norwegian Institute of Public Health released a statement saying that they had discovered a potentially significant mutation in the H1N1 influenza strain that could be responsible for causing the severest symptoms among those infected.

In the statement they said "The mutation could be affecting the virus' ability to go deeper into the respiratory system, thus causing more serious illness".

The World Health Organization said that the mutation did not appear to be widespread in Norway and the virus in its mutated form remained sensitive to antivirals and pandemic vaccines. A similar mutation had been detected in H1N1 viruses circulating in several other countries, including China and the United States, in severe as well as in some mild cases. "Although further investigation is under way, no evidence currently suggests that these mutations are leading to an unusual increase in the number of H1N1 infections or a greater number of severe or fatal cases."

On December 2, 2009 the WHO announced that they have been informed of two recent clusters of patients infected with oseltamivir-resistant H1N1 viruses. Both clusters, detected in Wales, UK and North Carolina, USA, occurred in a single ward in a hospital, and both involved patients whose immune systems were severely compromised or suppressed. Transmission of resistant virus from one patient to another is suspected in both outbreaks.

Resistance

As of December 2010, the World Health Organization (WHO) reported 314 samples of 2009 pandemic H1N1 flu tested worldwide have shown resistance to oseltamivir (Tamiflu). This is not totally unexpected as 99.6% of the seasonal H1N1 flu strains tested have developed resistance to oseltamivir. No circulating flu has yet shown any resistance to zanamivir (Relenza), the other available anti-viral.

Species affected

Swine

Before being transmitted to humans, an H1N1 type virus is known to have circulated in swine. In August 2007, about 25 people and 160 pigs developed flu at a county fair in Ohio. Analysis showed they were infected with the same strain—an H1N1 type containing genes of human, bird and swine origin. A 2004 study found that in Iowa, 20 percent of swine veterinarians and 3 percent of meatpackers, but no university workers, had antibodies in their blood indicating they had been infected with swine flu. Another study, of 804 rural Iowans, found that pig farmers were 50 times more likely, and their spouses about 30 times more likely, than university workers to carry swine flu antibodies. Pigs are also known to have been infected by humans.

Humans

Humans have been affected since early 2009. The November 27, 2009 worldwide update by the U.N.'s World Health Organization (WHO) states that "more than 207 countries and overseas territories or communities have reported laboratory confirmed cases of

pandemic influenza H1N1 2009, including over 7,820 deaths". The WHO has also tracked more than 622,482 laboratory-confirmed cases of H1N1.

Birds

In late August 2009, the government of Chile discovered that the human H1N1/09 virus had jumped, unmutated, to birds, "opening a new chapter in the global epidemic." Top flu and animal-health experts with the WHO and the CDC were monitoring the situation closely. They said the infected turkeys have suffered only mild effects, easing concern about a potentially dangerous development. Chile's turkey meat remains safe to eat, they said, and so far there have been no signs of a potentially dangerous mutation. Virus experts are concerned that a more dangerous and easily transmitted strain could emerge if H1N1/09 combines again with avian flu, which at present is far more virulent but much less contagious to humans. By October 2009, another outbreak at a turkey breeder was identified in Ontario, Canada.

Other animals

In October 2009, a ferret exhibiting flu symptoms was confirmed to have contracted the H1N1 virus from its owner in Oregon, USA. In November 2009, a case of novel H1N1 was confirmed in a household cat. The Oregon Veterinary Medical Association has confirmed the first cat fatality in the U.S. from the H1N1 virus. The association recommends that cat owners with flu symptoms avoid touching cat's eyes, nose, and mouth while sick. Thoroughly wash your hands after handling a sick pet since it may be possible for cats to transmit the virus to humans. This is the third confirmed case of H1N1 in a cat in the U.S.; other cases have occurred in Utah and Iowa. The first case of a dog with H1N1 was reported in December 2009.

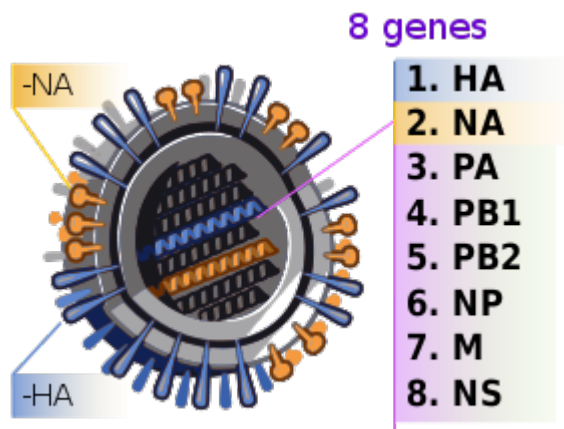
Nomenclature

The initial outbreak of a novel swine-origin H1N1 flu pandemic strain in 2009 was called by many names. In July 2009, WHO experts named it "pandemic H1N1/09 virus" to distinguish it from both various seasonal H1N1 virus strains and the 1918 flu pandemic H1N1 strain.

Some authorities object to calling the flu outbreak "swine flu". U.S. Agriculture Secretary Tom Vilsack expressed concerns that this would lead to the misconception that pork is unsafe for consumption. The CDC began referring to it as "Novel influenza A (H1N1)"; "A/H1N1" is sometimes used. The CDC has stopped using the nomenclature "novel H1N1" and has updated various web pages to reflect the change to "2009 H1N1 Flu". In the Netherlands it was originally called "pig flu" but is now called "Mexican flu" by the national health institute and in the media. South Korea and Israel briefly considered calling it the "Mexican virus". Later the South Korean press used "SI", short for "swine influenza". Taiwan suggested the names "H1N1 flu" or "new flu", which most local media adopted. The World Organization for Animal Health proposed the name "North American influenza". The European Commission adopted the term "novel flu virus".

Genetics

Genetic origins of the 2009 swine flu virus



HA	Hemagglutinin	swine (H1)	North America
NA	Neuraminidase	swine (N1)	Europe
PA	RNA polymerase subunit PA	avian	North America
PB1	RNA polymerase subunit PB1	human	1993 H3N2 strain
PB2	RNA polymerase subunit PB2	avian	North America
NP	Nucleoprotein	swine	North America
M	Matrix protein M1, M2	swine	Eurasia
NS/NEP	Non-structural proteins NS1, NEP (Nuclear Export Protein)	swine	North America

On April 24, 2009, the U.S. Centers for Disease Control and Prevention (CDC) determined that seven samples from suspected cases in Mexico matched the strain that had infected patients in Texas and California with no known linkages to animals or one another; the strain appeared to be spreading from human to human. The CDC determined that the strain contained genes from four different flu viruses – North American swine influenza, North American avian influenza, human influenza, and swine influenza virus typically found in Asia and Europe – "an unusually mongrelised mix of genetic

sequences." A CDC investigative team arrived in Mexico City on April 25, 2009 to work with Mexican counterparts to study the virus.

Pigs are susceptible to influenza viruses that can also infect both humans and birds, so they may act as a "mixing vessel" in which reassortment can occur between flu viruses of several species. Reassortment is a process that happens if two different types of influenza virus infect a single cell and it can produce a new strain of influenza. This is because the virus genome is split between eight independent pieces of RNA, which allows pieces of RNA from different viruses to mix together and form a novel type of virus as new virus particles are being assembled. This new strain appears to be a result of the reassortment of two swine influenza viruses, one from North America and one from Europe. But the North American pig strain was itself the product of previous reassortments, and has carried an avian PB2 gene for at least ten years and a human PB1 gene since 1993. These genes were passed on to the new virus.

Gene sequences for every viral gene were made available through the Global Initiative on Sharing Avian Influenza Data (GISAID). A preliminary analysis found that the hemagglutinin (HA) gene was similar to that of swine flu viruses present in U.S. pigs since 1999, but the neuraminidase (NA) and matrix protein (M) genes resembled versions present in European swine flu isolates. While viruses with this genetic makeup had not previously been found to be circulating in humans or pigs, there is no formal national surveillance system to determine what viruses are circulating in pigs in the U.S. So far, little is known about the spread of the virus in any pig population. A preliminary analysis has also shown that several of the proteins involved in the pathophysiology of the virus are most similar to strains that cause mild symptoms in humans. This suggests that the virus is unlikely to cause severe infections similar to those caused by the 1918 pandemic flu virus or the H5N1 avian influenza.

Late on May 6, 2009, Canada's National Microbiology Laboratory first completed the sequencing of Mexican samples of the virus, publishing the result to GenBank as A/Mexico/InDRE4487/2009(H1N1). This was later shown to be nearly identical to A/California/07/2009 (H1N1), the strain from California sequenced and published by the CDC on 27 April. Samples from Mexico, Nova Scotia and Ontario had the same sequence, ruling out genetic explanations for the greater severity of the Mexican cases.

The genetic divergence of the virus in samples from different cases has been analysed by Mike Worobey at the University of Arizona at Tucson, USA, who found that the virus jumped to humans in 2008 probably after June, and not later than the end of November. Worobey's research also indicated the virus had been latent in pigs for several months prior to the outbreak, suggesting a need to increase agricultural surveillance to prevent future outbreaks.

Chapter 5

2009 Flu Pandemic by Country

Pandemic (H1N1) 2009–2010 by country
Summary of official reports.^{††}

Country	Indicators/				Cases	Deaths
	Spread-Trend/ Intensity/Impact [‡]				Confirmed ^{††}	Confirmed
ECDC total						14,378
Reports Total					1,632,258	19,633
United States [^]	W =	**	mod	(113,690)	3,433	
Brazil	R -	*	mod	(58,178)	2,135	
India	W +	*	low	29,599	2,024	
Mexico	W +	**	mod	70,715	1,316	
China (mainland)				120,940	800	
Turkey	R +	**	mod	12,316	656	
Argentina	W -		low	(11,458)	626	
Russia	W +	**		25,339	604	
United Kingdom [#]	R =	*		(28,456)	474	
Canada	W +	**		(25,828)	429	
France [~]	R =	*	low	5,000	344	

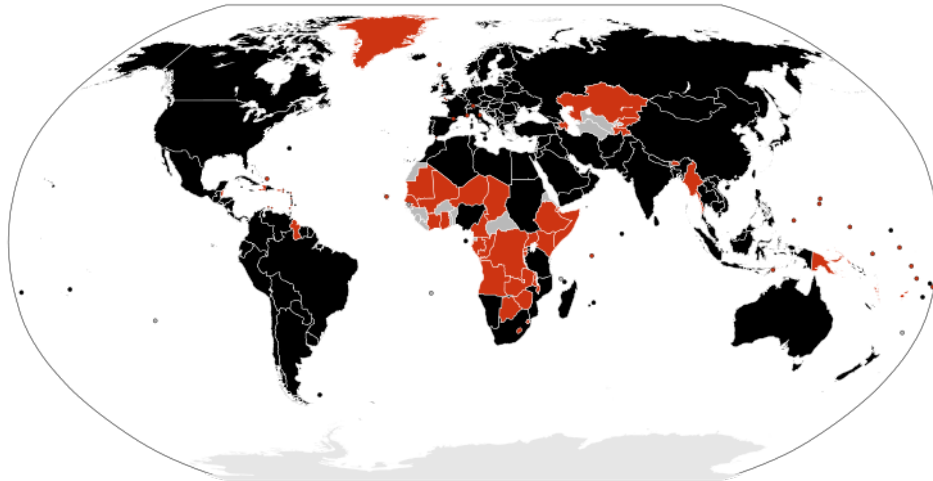
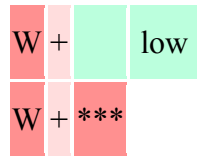
Spain	W + *	(1,538)	300
Egypt		15,812	278
Germany	N = low	(222,360)	258
South Korea	W + * low	107,939	250
Thailand	R = * low	31,902	249
Italy	W + **	3,333	244
Colombia	W + * mod	152,560	243
Peru	W - * low	9,165	223
Ukraine	R + ** mod	494	213
Ecuador	W - * low	2,251	200
Japan	W +	11,636	198
Australia	W -	37,484	193
Poland	W + ** mod	(2,024)	181
Chile	W = low2	12,258	156
Syria		(452)	152
Greece	N + *	(17,977)	149
Iran		3,672	147
Venezuela	W - * mod	2,187	135
Hungary	L + low	(283)	134
Saudi Arabia		14,500	128
Portugal	R + * low	(166,922)	122
Romania	W + * mod	6,999	122

Czech Republic	L +			2,445	102
Israel	W +	*	low	4,330	94
South Africa				12,640	93
Malaysia				12,210	92
Belarus	W +	**	mod	102	88
Serbia	R +	**	low	695	83
Hong Kong				33,109	80
Cuba	W +	**	mod	973	69
Costa Rica	W -	*	low	(1,867)	67
Morocco				2,890	64
Netherlands ⁺	W +	*	low	(1,473)	62
Bolivia	W -	*	low	2,310	59
Vietnam				11,186	58
Algeria				916	57
Finland	W +	**		6,122	56
Slovakia	S +		low	955	56
Paraguay	L -	**		855	54
New Zealand	L =	*	low	(3,199)	50
Taiwan				(5,474)	48
Sri Lanka	W +	*	low	642	48
Moldova				2,524	46
Palestinian Territories				1,676	43

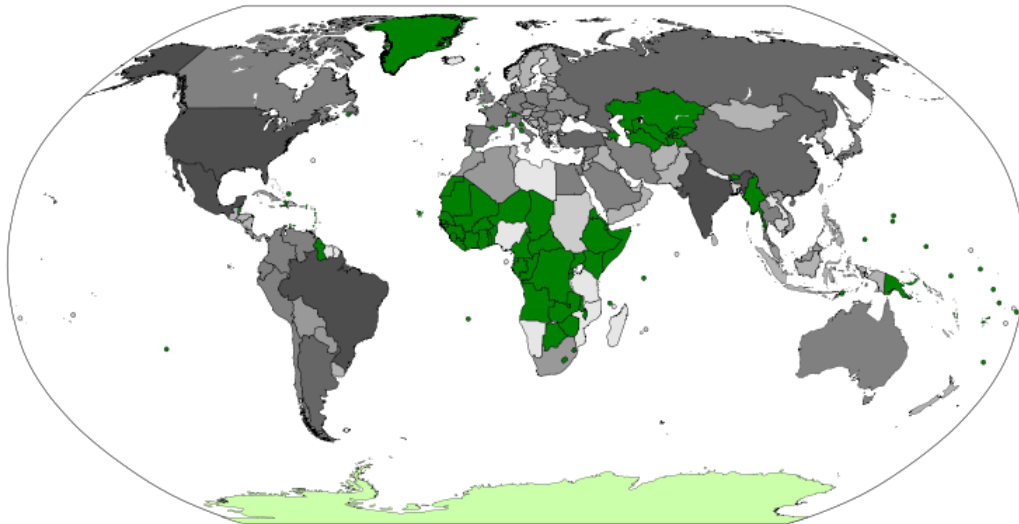
Iraq 2,880 42

Austria W + low (964) 40

Bulgaria W + *** 766 40

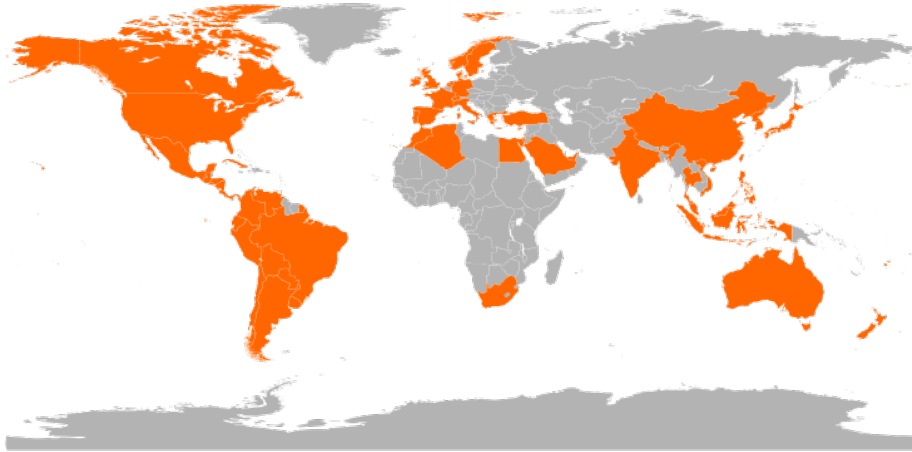


Confirmed cases followed by death
Confirmed cases
Unconfirmed or suspected cases

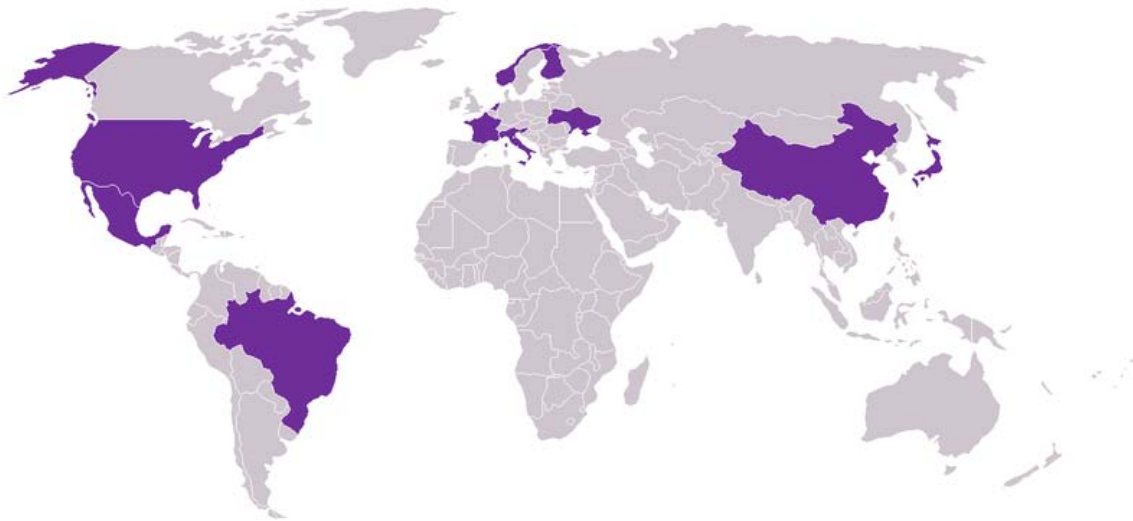


0 deaths
suspected deaths
1+ deaths

- 5+ deaths
- 10+ deaths
- 50+ deaths
- 100+ deaths
- 500+ deaths



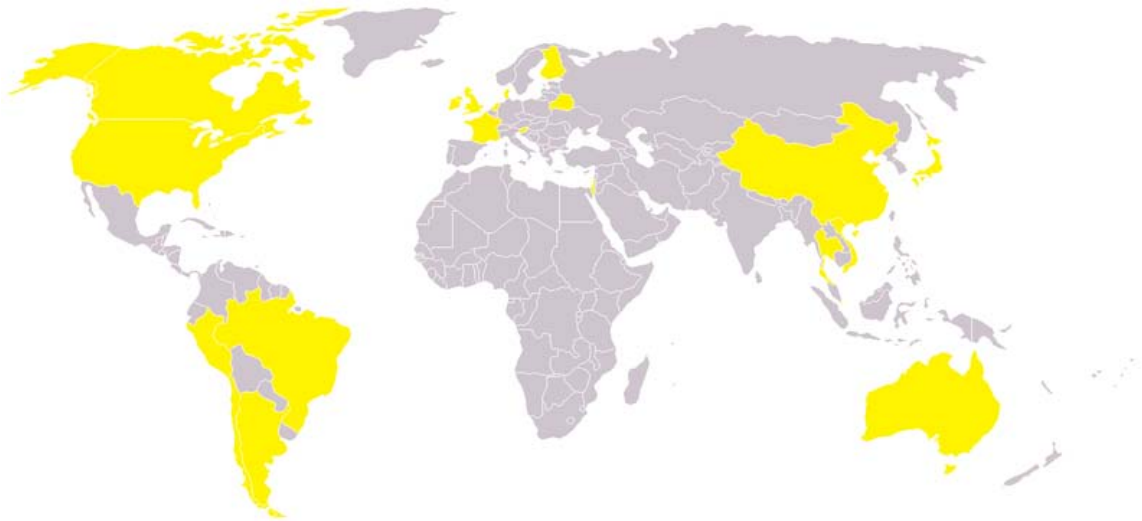
Confirmed community outbreaks



Confirmed mutation of H1N1 virus



▣ Confirmed double infections


















▣ Confirmed cases of tamiflu resistance

Overview

As the pandemic progresses, laboratory testing and confirmation may decrease. Confirmed figures for the United Kingdom, in particular, are only meaningful up to 2 July 2009, when routine testing stopped and presumed cases were treated without laboratory confirmation of diagnosis. Following the recommendations of the World Health Organization (WHO), many countries stopped issuing the numbers of the infected population, making this list inaccurate.

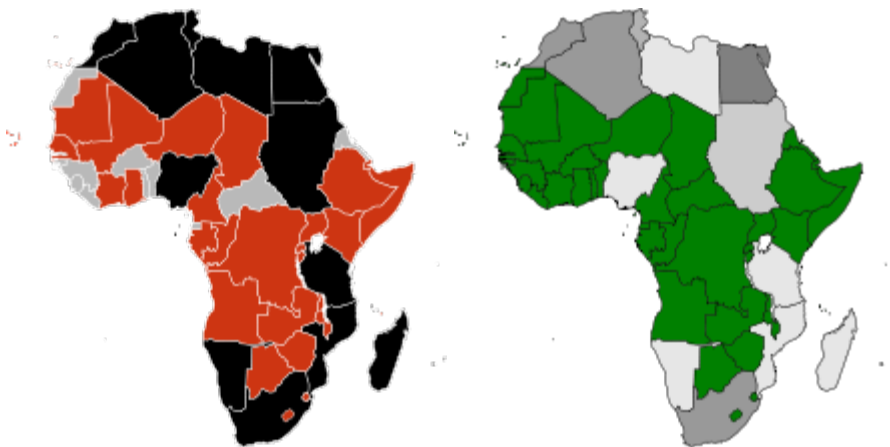
The ten countries and territories with most confirmed cases per capita

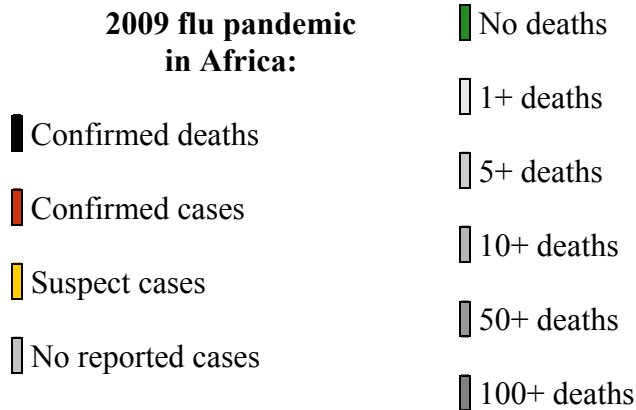
Pos.	Country	Population	Confirmed cases	Confirmed cases per 1,000 inhabitants
1	 Iceland	306,694	8,650	28.20
2	 Portugal	10,707,924	166,922	15.59
-	 Cook Islands	11,870	106	8.93
3	 Belgium	10,414,336	214,531	20.59
-	 Macau	559,846	2,625	4.68
-	 Hong Kong	7,055,071	31,554	4.47
4	 Spain	46,700,000	(155,051)	3.32
5	 Kuwait	2,691,158	8,622	3.20
6	 Brunei	338,190	972	2.87
-	 Jersey	91,626	234	2.55
7	 Germany	82,080,000	(192,348)	2.34
8	 South Korea	48,600,000	107,939	2.22
9	 Palau	20,796	46	2.21
-	 Cayman Islands	49,035	105	2.14
10	 Malta	405,165	718	1.77
	<i>World</i>	6,790,062,216	25,584,595	3.76

*Includes countries with over 40 confirmed cases only.

Affected continents/countries

Africa





The Egyptian government ordered the mass slaughter of all pigs in Egypt on April 29, even though the current strain is a human-human transmittable, human influenza that has already previously hybridized with avian and swine flu. The World Organization for Animal Health called the swine killing "scientifically unjustified".

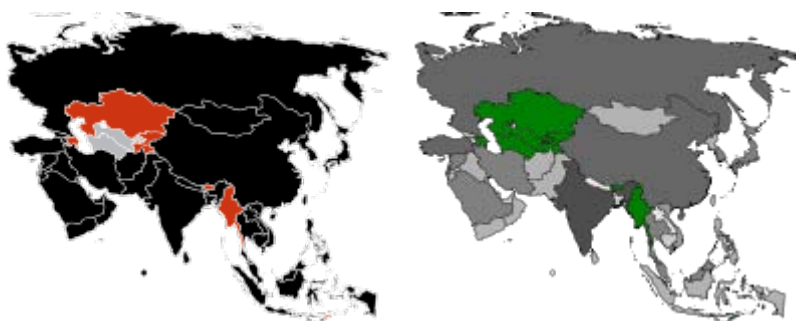
The first case of the novel H1N1 virus was discovered in Cairo, Egypt on June 2, 2009, in a 12-year-old girl coming from the USA with her mother. Only the girl was infected, and the officials caught the case before getting out of the airport. A second and third case were discovered on Sunday 7 June 2009, 2 students at the American University of Cairo.

On June 11, 2 more cases were discovered, bringing the total number of swine flu cases to 12 in Egypt.

The swine flu has been confirmed in 21 African countries: Egypt, South Africa, Morocco, Algeria, Tunisia, Ethiopia, Ivory Coast, Seychelles, Cape Verde, Libya, Kenya, Uganda, Botswana, Zimbabwe, Tanzania, Mauritius, Somalia, Sudan, Namibia, Zambia, Gabon, and Rwanda.

The H1N1 virus was a concern in the months leading up to the 2010 FIFA World Cup, which took place in June 2010 in South Africa.

Asia



**2009 flu pandemic
in Asia**

■ Deaths

■ Confirmed cases

■ Suspected cases

■ No reported cases

■ No deaths

■ 1+ deaths

■ 5+ deaths

■ 10+ deaths

■ 50+ deaths

■ 100+ deaths

Western and Central Asia



H1N1 in Central Asia

■ Deaths

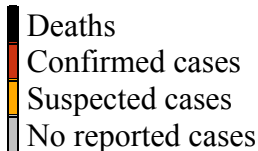
■ Confirmed cases

■ Suspected cases

■ No reported cases



H1N1 in Southwest Asia



On April 27, Azerbaijan imposed a ban on import of animal husbandry products from America. AZAL took additional safety measures and a sanitary quarantine unit of the Health Ministry started to operate in Heydar Aliyev International Airport with all aircraft and passengers being checked. On May 2 all checkpoints on borders with Russia passed to the medium security and disinfection barriers for both cars and pedestrians were installed at the Samur, Shirvanovka and Khan Oba checkpoints in Qusar and Khachmaz Raions. The veterinary services at checkpoints intensified their activities while hog farms in the northern regions passed to the closed farming regime.

Seventy-seven cases have been confirmed in Israel. In response to the outbreak, the Israeli Deputy Minister of Health, Yaakov Litzman, suggested out of respect for the religious sensibilities of Jews and Muslims, the flu should be called "Mexican Flu." This was done so as to not confuse the population into thinking that they could not acquire the virus if they did not eat pork. The Israeli government retracted this proposal following Mexican complaints.

The first confirmed cases of swine flu in Kuwait were reported on May 23, after about 18 people on U.S. military bases tested positive.

On May 30, 2009 three cases of swine flu were confirmed in Lebanon, the first in the country. "One Lebanese man who was in Spain and two Canadians who arrived in Lebanon a week ago are suffering from swine flu," the health minister said. "We put them in quarantine and the blood samples we have taken every day have proven to be positive. The Lebanese man and the two visiting Canadians -- a woman and her daughter -- were given the proper medical treatment in time and they are well now." The Lebanese Health Minister had previously asked citizens to stop the social habit of kissing. He also requested that affected schoolchildren be kept at home and that travel to countries in which cases have been confirmed be avoided. Beirut also banned the import of pork.

In Saudi Arabia, the first case of swine flu, which affected a Filipino nurse working at King Faisal Specialist Hospital and Research Center, was confirmed on June 1. The Health Ministry in cooperation with King Faisal Specialist Hospital and Research Center has applied the national plan for the prevention of Swine Flu in a manner that matches with the recommendations of WHO. Accordingly, the patient was isolated and provided with the required medical treatment. Arrangements are underway to examine those who were in contact with the patient to get sure that they are not infected. Saudi Arabia also took precautions and have currently closed all ISG (International Schools Group) schools after the eid holiday. In case they went back to their home country and contracted the virus. Schools will be closed till at least October 10.

Southern Asia



H1N1 in South Asia

- Deaths
- Confirmed cases
- Suspected cases
- No reported cases



H1N1 in Southeast Asia

- Deaths
- Confirmed cases
- Suspected cases
- No reported cases

All people entering India via the main airport hubs of Mumbai, New Delhi, Kolkata, Ahmedabad, Goa, Jaipur, Kochi, Chennai, Bangalore and Hyderabad are being screened. The primary focus is on passengers entering from the United States of America, The United Kingdom, Canada, Mexico, France, and New Zealand. As of 25 October 2009, over 13000 cases have been confirmed in India with 444 deaths, starting with a 13-yr old girl's death in the city of Pune, where almost 91 people died in the city.

In the Maldives, a ministerial committee has been established to supervise swine flu preventive measures to avoid an outbreak. All visitors arriving at the Malé International Airport on Hulhule Island and the country's three commercial seaports are being screened.

Pakistan has taken precautionary measures at the international airports to check passengers coming from swine flu affected countries. Doctors are checking the incoming passengers and allow entry only to those with no flu symptoms. The major hospitals in all the big cities are on high alert.

Southeastern Asia

Since 8 July 2009 a total of 207 cases of A(H1N1) flu have been reported in Brunei.

Cambodia's health authorities remain alert but confident that the country is prepared for a swine flu pandemic. In terms of ensuring that infected pigs do not spread the disease to Cambodia, the Cambodian Pig Raiser Association said it has told the government it should ban live pig imports. But Khlauk Chuon, the deputy director of Camcontrol at the Ministry of Commerce, said they would only ban live pig imports from a country that has been hit with swine flu.

The Indonesian government halted the importation of pigs and initiated the examination of 9 million pigs in Indonesia. Thermal scanners which can detect human body temperature have been installed at Indonesian ports of entry.

The Lao government bought 10 thermal imaging machines to install at the country's major immigration border checkpoints. The Prime Minister Bouasone Bouphavanh said masks should be made available and health officials would be assigned to work at border checkpoints. On 22 July, Laos recorded its first death from influenza A(H1N1).

In Malaysia, health screenings were carried out on passengers traveling to and from Mexico via sea, air and land beginning April 17. The Health Ministry's disease control division activated its operations room to monitor the swine flu situation and informed medical practitioners treating suspicious cases to inform the district health office immediately. Thermal scanners were installed at Kuala Lumpur International Airport. Screenings were imposed in Pengkalan Hulu, at the border with Thailand, in late April. Quarantine rooms had been allocated in 28 hospitals, and the country has stockpiled more than 2 million doses of Tamiflu, as of May 2009. Schools were issued strict hygiene procedures on May 16 to contain any H1N1 outbreak among students and teachers. On May 15, the Health Ministry confirmed Malaysia's first case of A (H1N1) infection of a male student who had arrived via air from Newark. The first A(H1N1) related death was reported on 23 July 2009. As of August 11, 2009 there has been 2,253 confirmed cases in Malaysia. As of August 12, 2009 the total number of A(H1N1) related deaths in Malaysia stands at 44.

In Myanmar, Chairman of Global Human Flu Prevention and Response Work Committee Deputy Minister for Health Dr Mya Oo inspected preventive measures against the human flu at Yangon International Airport on May 1.

In the Philippines, thermal imaging equipment at airports was implemented to screen passengers coming from the US for flu symptoms. The Philippines may quarantine travelers arriving from Mexico with fevers. Also, the importation of hogs from the U.S. and Mexico was banned, and the restriction of swine influenza vaccine use was retracted. On May 18, 2009, a Filipina girl who arrived from Houston, USA was the first confirmed case of H1N1 virus in the Philippines. As of June 15, 2009, there were 193 confirmed cases. By June 22, first known death was reported.

The first case of Influenza A (H1N1-2009) in Singapore was confirmed on May 27, 2009. It was announced on June 18, 2009 that Singapore appeared to have its first case of local infection of the A(H1N1) virus. As of July 7 there have been reported 1,217 confirmed cases of A(H1N1) in Singapore. As of July 25, there were 4 confirmed deaths related to A(H1N1) virus in Singapore.

Vietnam's Ministry of Health released an emergency dispatch and urged agencies to take precautionary measures against swine flu. Thermal imaging devices were dispatched to airports and border gates to screen passengers. In response to WHO's warnings, Vietnam on April 30, 2009 raised its swine flu alert level to 4 which indicated a "threat of

community level outbreaks" while local authorities have been executing precautionary measures. On May 1, 2009 an Vietnam's Ministry of Industry and Trade official said that Ministry was considering a ban on pork import "under certain situations" to prevent swine flu from entering Vietnam. As of May 31, 2009. The Government of Vietnam announced its First new case of A(H1N1) virus in the Country. A 23 years old Vietnamese student who recently returned from the United States has tested positive for swine flu.

Eastern Asia



H1N1 in Eastern Asia

- Deaths
- Confirmed cases
- Suspected cases
- No reported cases

On April 26, it was announced that visitors returning from flu-affected areas to China who experienced flu-like symptoms within two weeks would be quarantined. May 2, the Chinese government suspended flights from Tijuana to Shanghai. Meanwhile, the Civil Aviation Administration of China also assigned a charter to transport stranded Chinese visitors back home. The first suspected case found on mainland China was reported on May 10, 2009.

On April 29, 2009 the Food and Health Bureau of Hong Kong advised Hong Kong residents not to travel to Mexico unless absolutely necessary. The first case reported was a Mexican who flew in from Shanghai. The Bureau also escalated the alert level from "alert" to "serious", which activated health protection measures in all ports of entry of Hong Kong. As such, temperature screening machines are used at all checkpoints to identify passengers with fever and respiratory symptoms. Any passenger who fails the temperature test and confirmed having a fever will be quarantined and sent to public

hospital for further investigation. Hong Kong also became one of the first jurisdictions to declare the swine flu as a notifiable disease, and much of the procedures against the spread of the swine flu were learned from the 2003 SARS outbreak, of which Hong Kong was the epicenter of the outbreak. On May 1, one case became the first confirmed case of swine flu in Hong Kong and also the first in Asia. The Mexican patient arrived in Hong Kong on April 30. Metropark Hotel Wanchai, where the patient stayed, was quarantined. After the first swine flu case was confirmed by laboratory, Hong Kong's response level was raised from "serious" to "emergency".

In Japan, any live pigs being brought into the country were inspected to ensure they were not infected with the influenza. Japanese Agriculture Minister Shigeru Ishiba appeared on television to reassure customers that it is safe to eat pork. The Japanese farm ministry said that it would not ask for restrictions on pork imports because the virus was unlikely to turn up in pork, and would be killed by cooking. On 8 May, the first three cases were confirmed. The infected patients had spent time in Canada and returned to Japan via Detroit. The first domestic infection was confirmed on 16 May in Kobe. As of 18 May, 130 cases had been confirmed.

South Korea warned against travel to Mexico City and three Mexican states. The government has also stepped up quarantine and safety checks on travelers arriving from the United States and Mexico, and pork imports from those countries. An emergency quarantine system is also in place, with simple tests conducted on people arriving with flu symptoms at airports. On April 28, South Korea reported its first probable case of swine flu after positive preliminary tests on a nun who had recently returned from a trip to Mexico. Several sources have informed that one case has been confirmed by lab in South Korea, on April 30. On May 2, the first suspected woman turned out to be infected with the influenza A subtype H1N1. South Korea became the second infected nation in Asia. On September 13, five people died, and 1 person got a brain death. As of November, 107,939 have been infected.

On May 20, 2009, the first case of the influenza has been confirmed in Taiwan. The government had previously taken several steps to prevent the possible outbreak of Swine Flu, including a command center set up, travel alerts for infected nations, and more severe health check been conducted at international ports. Taiwan said visitors who came back from affected areas with fevers would be quarantined. According to The Department of Health (DOH), Taiwan has a sufficient supply of surgical masks and vaccine to deal with the flu. The DOH also stated that they have 50 million to 60 million masks in stock and local manufacturers have the capability of producing 200,000 doses of the flu vaccine a month. In an effort to prevent the entry of the swine influenza, the Centers for Disease Control has announced on April 28 that every flight from the Americas, specifically Canada and the United States, that arrives in Taiwan from April 29 and onward will be subject to a strict on-board screening procedure.

On July 2, the first case of oseltamivir-resistant virus in Asia was announced in Japan, in a woman who had been taking Tamiflu prophylactically.

On July 18, 2009, Hong Kong had its first swine flu death.

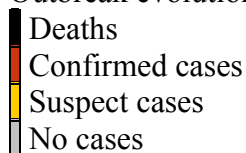
On July 3, a case of Tamiflu-resistant virus was discovered in a woman suffering from the flu. The woman had not previously taken Tamiflu, so concern has been expressed that she may have contracted an already resistant virus from someone else.

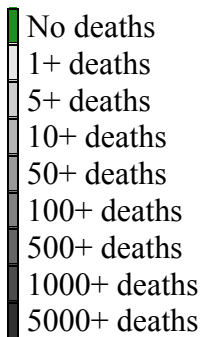
On 28 August 2009, the Japanese Ministry of Health, Labour and Welfare announced that it estimated approximately 760,000 people would be infected and 46,400 hospitalized per day during the expected peak time of October 2009. Overall they predict 20% of rural Japanese to become infected and 30% in city areas.

Europe



Outbreak evolution in Europe:





On April 27, the Spanish Ministry of Health and Social Policy announced that a man in Castilla-La Mancha who had recently returned from Mexico had contracted the disease. The man, aged 23, had returned from Mexico on April 22 and had been quarantined on the 25th. This was the first confirmed case in Europe.

On April 27, the European Union health commissioner advised Europeans not to travel to the United States or Mexico unless urgent. This followed the discovery of the first confirmed case in Spain.

On June 14, It was reported that the United Kingdom had its first confirmed swine flu related death. The individual was a Scottish woman named Diana Barnett.

As of December 22, every European country, apart from the 5 microstates have confirmed deaths due to swine flu. France has 27 confirmed deaths; Spain has 33 confirmed deaths; Norway has 29 confirmed deaths (Jan 4, 2010); Italy has 6 confirmed deaths; Belgium and Germany have 8 confirmed deaths; Sweden has 3 confirmed deaths (Nov 3); Malta and Greece has 3 confirmed deaths; Denmark, Finland , Hungary and Luxemburg all have one confirmed death; Ireland and the Netherlands have 10 confirmed deaths each and the United Kingdom has 79 confirmed deaths along with the British government suggesting 55,000 new case of Swine Flu reported in the week up to the 16th of July 2009. The British government has also warned that deaths from swine flu this winter could be between 19,000 and 65,000 in the UK alone.

Hungary reported the first death in the country on July 22. Ireland reported its first death on August 7.

As of August 19, all European countries with the exception of the micro states San Marino and Vatican City have reported confirmed cases.

North America



Outbreak distribution in North America:

■ Deaths

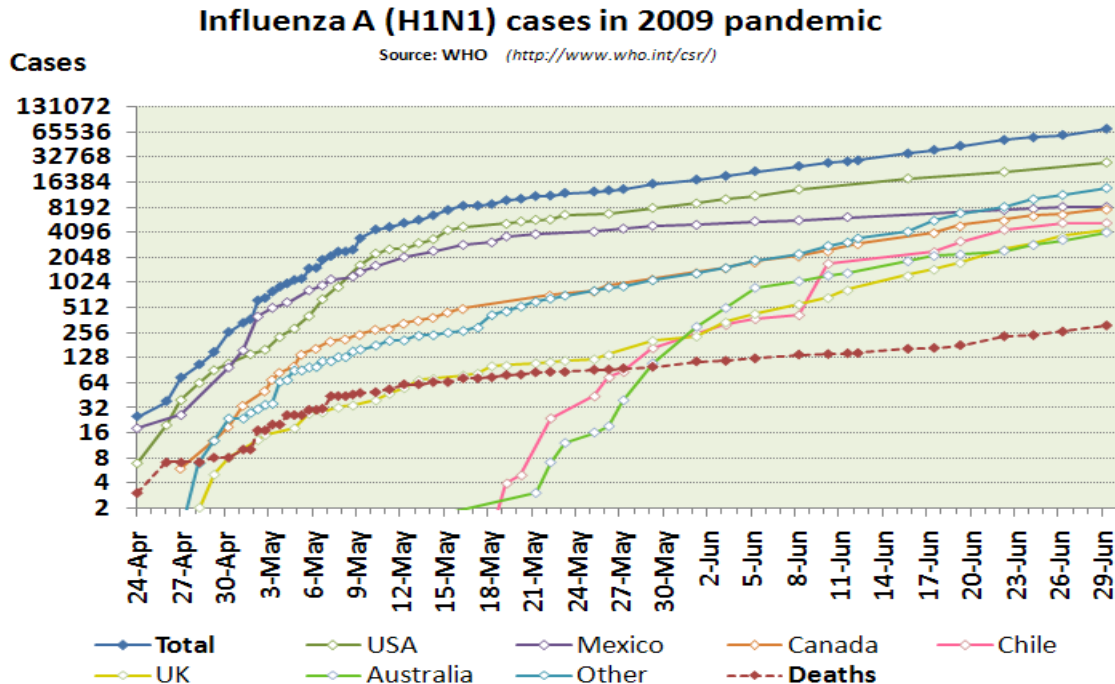
- Confirmed cases
- Suspect cases
- No cases



- No deaths
- 1+ deaths
- 5+ deaths
- 10+ deaths
- 50+ deaths
- 100+ deaths
- 500+ deaths
- 1000+ deaths
- 5000+ deaths

In Canada, roughly 10% of the populace has been infected with the virus, with 363 confirmed deaths (as of December 8, 2009); there were over 10,000 confirmed cases when Health Canada stopped counting in July 2009. Canada began its vaccination campaign in October and 25% of the populace has since been immunized against H1N1, with Canada leading the world in the percentage of the population vaccinated. The pandemic was a concern in the months leading to the XXI Olympic Winter Games, which took place in Vancouver on February 2010.

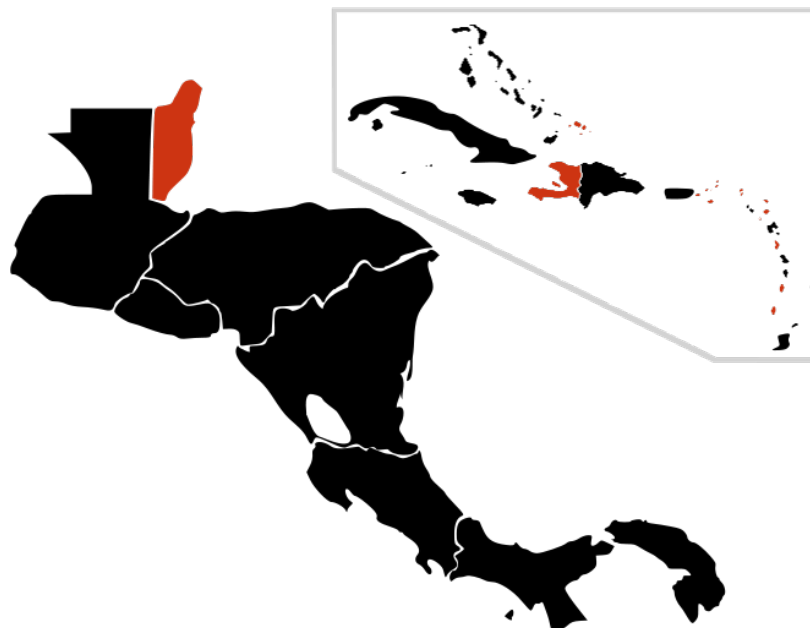
Dr. José Ángel Córdova Villalobos, Mexico's Secretariat of Health, stated that since March 2009, there have been over 1,995 suspected cases and 149 deaths, with 20 confirmed to be linked to a new swine influenza strain of Influenza A virus subtype H1N1. "As many as 23,000 Mexicans were likely infected with the swine flu virus,' Neil Ferguson of Imperial College London and colleagues reported in the journal Science." Soldiers mobilized by the government have handed out six million surgical masks to citizens in and around Mexico City. On April 24, 2009, schools (from pre-school to university level) as well as libraries, museums, concerts and any public gathering place, were shut down by the government in Mexico City and the neighboring State of Mexico to prevent the disease from spreading further; the schools in Mexico City, the State of Mexico, and the state of San Luis Potosí will remain closed until at least May 5. Marcelo Ebrard, Mexico City's mayor, has also asked all night-life operators to shut down their places of business for ten days to prevent further infections. On April 25, President Felipe Calderón declared an emergency which granted him the power to suspend public events and order quarantines. On April 26, the World Bank announced US\$ 25 million in immediate aid loans to Mexico, an additional US\$ 180 million for long-term assistance to address the outbreak, and advice on how other nations have responded to similar crises. On April 27, the Secretariat of Public Education announced that all schools in Mexico will remain closed at least until May 6. On April 28, the Mexico City government closed all restaurants and cinemas. The National History and Anthropology Institute also closed all its archaeological sites and museums, including the most famous Mayan and Aztec ruins, until further notice.



A semi-logarithmic chart of laboratory-confirmed A(H1N1) influenza cases by date according to WHO reports. Mexico, USA, and Canada are shown as a breakdown of the total.



In the United States, initial reports of atypical flu in two individuals in southern California led to the discovery of the novel swine flu virus by the CDC in mid-April. More than a hundred cases were confirmed in the next two weeks, spread through a dozen states. Outside of California and Texas, initial cases were all tied to recent travel to Mexico or close contact with those who had recently visited Mexico. St. Francis Preparatory School, a private school in New York, was the center of a large cluster of cases after a Spring Break trip by several students, and perforce one of the first U.S. schools to be closed as a public health measure during the early outbreak. Most of the cases in California and Texas are not linked and may reflect localized outbreaks of this virus in those areas. The disease was not as virulent outside of Mexico as within Mexico, for reasons not fully understood. The US declared a state of Public Health Emergency but this was said to be standard procedure in cases as divergent as the recent inauguration and flooding. On April 29, the US suffered its first confirmed death of swine flu, and on May 5 the first US citizen died from swine flu. As of June 6, there were 17 confirmed deaths from swine flu in the US. As of mid-May 2009 many states had abandoned testing for likely influenza cases unless serious illness and/or hospitalization were present. Because reported numbers represent only confirmed cases, they are a "very great understatement" of the total number of cases of infection, according to the CDC. The real number of swine flu cases in the United States could be 「upwards of 100,000,」 a top public health official estimated on Friday — far higher than the official count of 7,415 cases confirmed by laboratories. As of October 20, 2009, swine flu cases have reached over 256,000, with 2,800 deaths in the United States.

Caribbean



H1N1 in Caribbean and Central America

- █ Deaths
- █ Confirmed cases

 Suspect cases
 No cases

In Aruba, all passengers arriving by airplane or cruise ship were required to fill out a health questionnaire beginning on April 27, 2009. Hotels and resorts are required to report to authorities if any tourists are showing flu-like symptoms. The government of Aruba also ordered antiviral medication and other supplies from the Netherlands and the United States. No swine flu cases have been reported.

In Barbados, the first confirmed case of the H1N1 virus occurred on June 3, 2009. The second case was confirmed on June 6. The third case was confirmed on June 10. The fourth case was confirmed on June 17. Twenty five outstanding samples have been sent to the Caribbean Epidemiology Center, the results of which would confirm if there is in-country transmission.

Cuba suspended flights to and from Mexico for 48 hours. The first case of swine flu in Cuba was confirmed in mid-May.

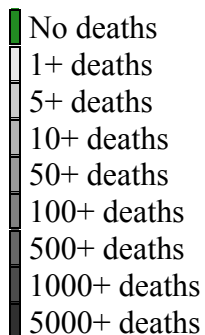
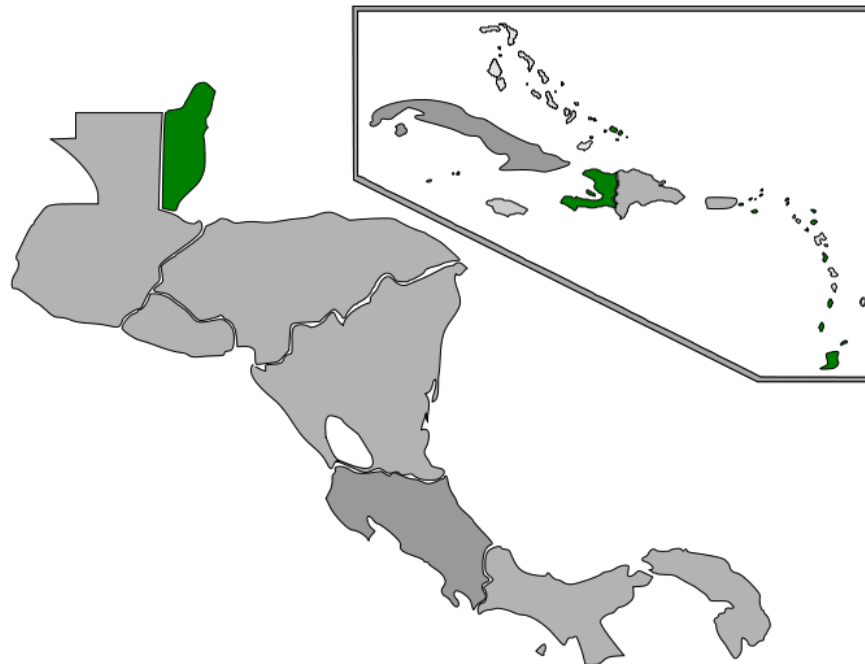
The first two cases in the Dominican Republic were confirmed on May 27. On June 5, a 17 year old pregnant girl infected with the AH1N1 virus died. 93 cases were confirmed to this date.

As of 7 July 2009, there has been 33 confirmed cases of swine flu in Jamaica. Health Minister Ruddy Spencer told Parliament that the country has been placed on high alert. There has been heightened surveillance at health care facilities and port entry's.

In Trinidad and Tobago, one female has been confirmed as having contracted the H1N1 influenza.

In the Bahamas, ten students and teachers who arrived from Mexico in the last week of April are in quarantine.

Central America



The first two cases of the 2009 flu pandemic in Costa Rica, both of whom had traveled to Mexico, were confirmed on April 28. On July 31 local authorities announced that the country was selected among the sample countries that will be part of the test of the vaccine developed by Swiss pharmaceutical Novartis. The local sample will include 784 Costa Ricans ages 3 to 64. Besides Costa Rica, this vaccine prototype will be tested also in Mexico and the United States.

On August 11, it was confirmed that Costa Rica's President, Óscar Arias Sánchez, was infected with the A(H1N1) virus, becoming the first head of state sick with the A(H1N1) virus. President Arias return to his normal activities after one week of isolation at his home. As of October 15 the Costa Rican Ministry of Health had 1,530 confirmed cases, 1,242 pending cases, 7,404 already discarded, and 38 deaths.

Guatemala is checking all travelers arriving from Mexico for signs of flu and stopping anyone with symptoms of the virus at border crossings. On May 5, in a meeting with

Health Minister and the Vicepresident, it was announced that an 11-year-old girl was infected with the AH1N1 virus. As of July 7 the Guatemala had 286 confirmed cases leading to two fatalities.

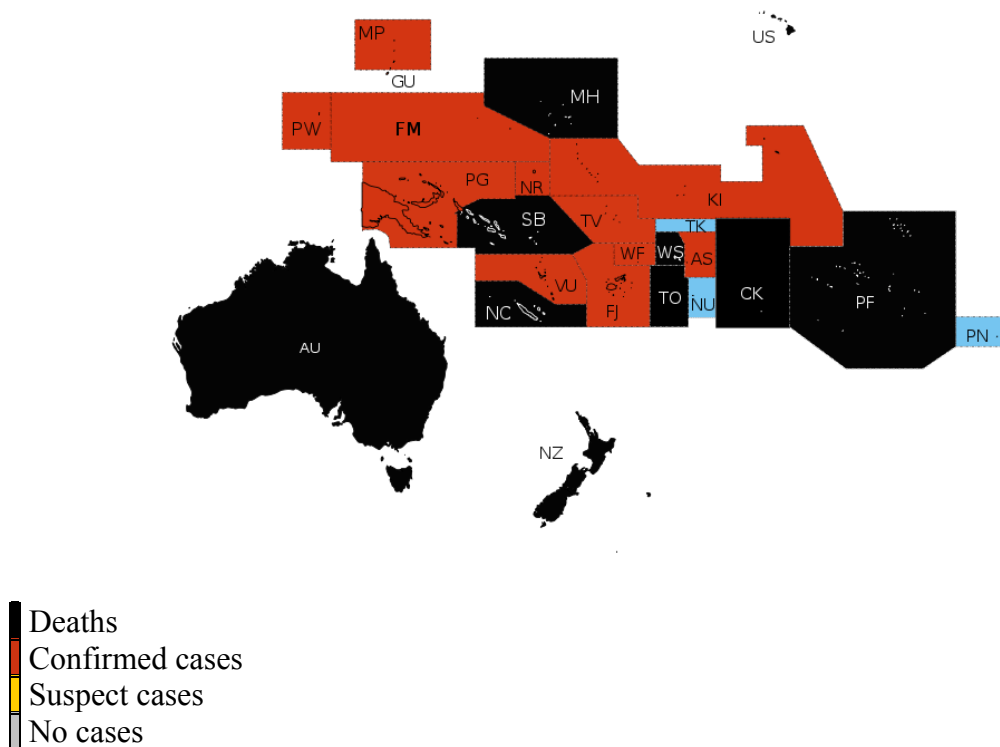
Honduras reported its first confirmed case of A(H1N1) flu on 27 May 2009. By June 7 the country had reported 67 cases, most of the cases on the city of San Pedro Sula and the Atlantic Coastline. There are few cases on other cities and areas. All airports and commercial sites as well as public events are monitored. As of July 7 there were 123 confirmed cases and one fatality.

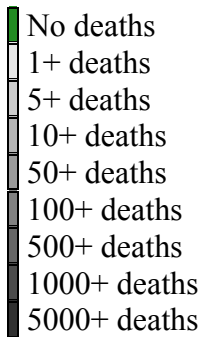
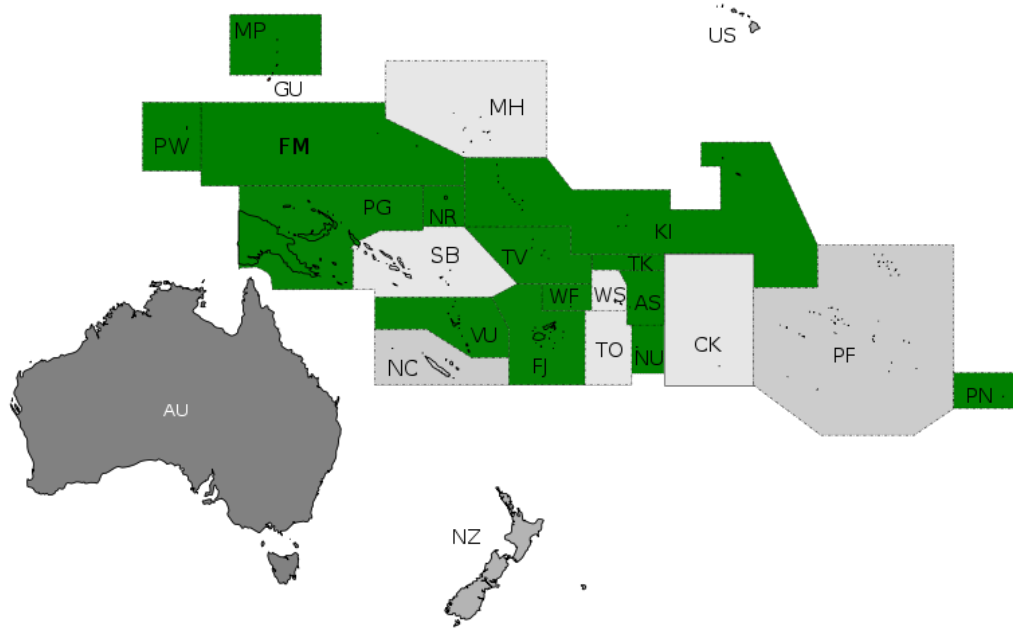
As on June 4, 179 confirmed cases had been reported by Panamanian health authorities. Of these, 91 were male and 88 were female. Schools with positive cases are being disinfected. Thermal cameras had been deployed in Tocumen International Airport to identify sickness among arriving passengers.

As of July 7, El Salvador reported 319 confirmed cases, and Nicaragua 321. Panama and Nicaragua have not reported any fatalities.

Oceania

Researchers in Australia and New Zealand have reaffirmed that infants under the age of 1 year have the highest risk of developing severe illness from swine flu. Canadian health officials have reported that swine flu is hospitalizing three to four times as many children as regular seasonal flu.





The first confirmed case in Australia was reported on May 9. As of July 3, 2009, Australia has 7,290 confirmed cases. The first Australian death was on June 19 and the total death toll has risen to 20. The alert level has been lifted from "delay" to "contain", giving authorities in all states the option to close schools if students are at risk. Australia has a stockpile of 8.7 million doses of Tamiflu and Relenza. At the beginning of the outbreak airlines were required to report passengers from the Americas with influenza symptoms, and nurses were deployed at international airports.

On May 30, New Zealand had 9 laboratory confirmed cases and 10 probable cases. All patients recovered. Over the month of June cases in New Zealand rose rapidly. On June 14 the Ministry of Health announced a 65% increase in cases in just 24 hours. On July 4, the Ministry of Health announced the first New Zealand deaths. There have been three confirmed deaths of patients who had tested positive for the flu, however two of them had known underlying medical conditions. The total number of confirmed cases has now reached 945.





Islands and Antarctica

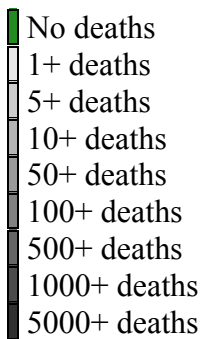
No cases have been reported in Antarctica. Two cases were confirmed in the Pacific Islands. Both cases were confirmed on June 15, one in the Solomon Islands and another in Samoa. 5 cases has been confirmed in Fiji as of June 24 and 1 case in Vanuatu.

South America



Outbreak evolution in South America:

-  Deaths
-  Confirmed cases
-  Suspected cases
-  No reported cases



In Argentina, as of April 2009, passengers with influenza symptoms arriving from Mexico and United States were required fill out a form to be located should they experience any symptoms. In addition, the government has also stepped up safety checks, and thermal scanners are being used on airports to detect passengers with fever and other influenza symptoms. Flights from Mexico were also temporarily suspended as a precautionary measure. These measures however have proven to be largely ineffective.

As of June 22, Argentina had 1,213 confirmed cases of swine flu and 10 confirmed deaths, increasing to 52 confirmed deaths and an estimated number of as many as 100,000 affected people on July 2, as confirmed by the then newly appointed Minister of Health Juan Luis Manzur. As of July 14, the number of officially recognised cases skyrocketed, with 137 deaths, making the death toll in Argentina the second highest in the world, only behind the United States and surpassing that of Mexico.

As of April 2009, Brazilian airports would monitor travelers arriving from affected areas, under the direction of the National Sanitary Surveillance Agency (ANVISA). Air crews were trained on signs and symptoms of swine influenza so that passengers displaying symptoms would receive guidance from ANVISA upon arrival. As of June 4, there were 28 confirmed cases of swine flu in Brazil.

The first case of A(H1N1) flu in Chile was confirmed on May 17. On May 29, the Chilean Health ministry confirmed the number of cases of A-H1N1 had risen to 224., the same day two more cases were confirmed. On June 3 Chile suffered its first confirmed death of swine flu, a 37-year-old man from Puerto Montt. To the date, and since the laboratory tests are no longer mandatory, the estimation of cases in Chile go up to 500.000 cases.

On May 3, 2009, Minister Palacio confirmed the first case of A(H1N1) in Colombia, in a 42-year-old person from Zipaquirá, who recently travelled to Mexico. According to Palacio, only one out of 18 tests sent to Atlanta was positive. The patient was isolated and put under medical treatment. On the same day, Palacio stated there were 108 suspect cases in the country. On April 27, the Government declared a "national disaster" state in order to face the emergency, which allowed health authorities to have a special budget to do so. The government purchased 400,000 oseltamivir (Tamiflu) doses, which will be distributed through the Social Protection ministry to the affected if there are confirmed cases.

Health officials are carrying out checks on people with flu symptoms entering the country from sea or air. On April 29, Ecuador closed its borders to Mexican citizens and foreigners of other nationalities arriving from Mexico for a period of 30 days. On May 15, Health officials confirmed the first case of AH1N1 flu in Ecuador . On May 20, the Health Department confirmed 7 more new cases of AH1N1, raising the total number of infected people to 8, the number has now risen to 41.

The first case of swine flu in Peru was confirmed on n May 14. On May 17, the second case was confirmed, an American-born man residing in Arequipa. He had returned from the US on May 12, not showing any symptoms until two days later. On May 18 a new case was confirmed, a scholar returning from a trip to Dominican Republic, that studied in the Altair school. another case of a scholar from the same trip to Dominican Republic. Student had contact with 3rd victim and both studied in the same school. The Governor of Callao ordered that all passengers from any infected country be checked before their arrival on Peruvian territory. Also, the Peruvian government must be warned of any case or symptom of fever. This step is in order to prevent any infections, since the main port

and airport of Peru are located in Callao. Also, the government has prepared a special area at the Hospital "Daniel Alcides Carrión" to treat cases of this disease. Efforts are being made to examine slaughterhouses and they are screening incoming passengers from problem areas. All commercial flights from Mexico to Peru were suspended on April 29.

In Venezuela, controls have been raised at airports to prevent contagion from spreading. Travellers from the United States and Mexico with flu symptoms are being isolated until they are given the all clear. Pig farms in the country are being "closely inspected" and stockpiles of medicines built up. On May 28 the Health Minister, Jesús Mantilla, confirmed the first case of the A/H1N1 flu in a Venezuelan citizen who arrived in a flight from Panama. He was isolated to the place he is receiving treatment and his condition is stable. The following day, a second case was confirmed from another person who also arrived from the same flight.

Reporting bias

Epidemiologists caution that the number of cases reported in the early days of an outbreak can be very inaccurate and deceptive. This can be due to several causes, including selection bias, media bias, and incorrect reporting by governments.

One selection bias in epidemiology pertains to authorities in different jurisdictions looking at different sets of patient populations. For example, in the early days of the pandemic, doctors in Mexico may have been concentrating on patients in hospitals, rather than the larger vulnerable population, which may in part explain the higher mortality recorded in the country. Conversely, it is implausible that few, if any, have died in Mexico in recent months when Brazil and the United States have accumulated hundreds of additional lab-confirmed deaths in the same period. Media bias in reporting swine flu cases and deaths may skew incidence maps based on these media reports. Countries with poor health care systems and poor laboratory facilities may take longer to identify suspected cases, analyse those cases, and report them. Passive data collection methodologies (waiting for the patient to arrive at a health care facility) are considered inferior to active data collection techniques (performing random stratified sampling) due to various forms of selection bias. and because laboratory facilities to perform swift genetic tests on patient samples are not widely available. As of July 2009 there are no properly controlled epidemiological studies for the 2009 swine flu outbreak.

Chapter 6

2009 Flu Pandemic Vaccine

The **2009 flu pandemic vaccines** are the set of influenza vaccines that have been developed to protect against the pandemic H1N1/09 virus. These vaccines either contain inactivated (killed) influenza virus, or weakened live virus that cannot cause influenza. The killed vaccine is injected, while the live vaccine is given as a nasal spray. Both these types of vaccine are usually produced by growing the virus in chicken eggs. Around three billion doses will be produced annually, with delivery from November 2009.

In studies, the vaccine appears both effective and safe, providing a strong protective immune response and having similar safety profile to the normal seasonal influenza vaccine. However, about 30% of people already have some immunity to the virus, with the vaccine conferring greatest benefit on young people, since many older people are already immune through exposure to similar viruses in the past. The vaccine also provides some cross-protection against the 1918 flu pandemic strain.

Early results (pre-25 December 2009) from an observational cohort of 248,000 individuals in Scotland have shown the vaccine to be effective at preventing H1N1 influenza (95.0% effectiveness [95% confidence intervals (CI) 76.0-100.0]) and influenza related hospital admissions (64.7% [95%CI 12.0-85.8]).

Developing, testing, and manufacturing sufficient quantities of a vaccine is a process that takes many months. According to Keiji Fukuda of the World Health Organization (WHO), "There's much greater vaccine capacity than there was a few years ago, but there is not enough vaccine capacity to instantly make vaccines for the entire world's population for influenza." Nasal mist version of the vaccine started shipping on October 1, 2009.

Types of vaccine

Two types of influenza vaccines are available:

- TIV (flu shot (injection) of **t**ri**v**alent (three strains; usually A/H1N1, A/H3N2, and B) **i**nactivated (killed) vaccine) or
- LAIV (nasal spray (mist) of **l**ive **a**ttenuated **i**nfluenza vaccine.)

TIV works by putting into the bloodstream those parts of three strains of flu virus that the body uses to create antibodies; while LAIV works by inoculating the body with those same three strains, but in a modified form that cannot cause illness.

LAIV is not recommended for individuals under age 2 or over age 49, but might be comparatively more effective among children over age two.

Manufacturing methods

For the inactivated vaccines, the virus is grown by injecting it, along with some antibiotics, into fertilized chicken eggs. About one to two eggs are needed to make each dose of vaccine. The virus replicates within the allantois of the embryo, which is the equivalent of the placenta in mammals. The fluid in this structure is removed and the virus purified from this fluid by methods such as filtration or centrifugation. The purified viruses are then inactivated ("killed") with a small amount of a disinfectant. The inactivated virus is treated with detergent to break up the virus into particles, and the broken capsule segments and released proteins are concentrated by centrifugation. The final preparation is suspended in sterile phosphate buffered saline ready for injection. This vaccine mainly contains the killed virus but might also contain tiny amounts of egg protein and the antibiotics, disinfectant and detergent used in the manufacturing process. In multi-dose versions of the vaccine, the preservative thimerosal is added to prevent growth of bacteria. In some versions of the vaccine used in Europe and Canada, such as *Arepanrix* and *Fluad*, an adjuvant is also added, this contains a fish oil called squalene, vitamin E and an emulsifier called polysorbate 80.

For the live vaccine, the virus is first adapted to grow at 25 °C (77 °F) and then grown at this temperature until it loses the ability to cause illness in humans, which would require the virus to grow at our normal body temperature of 37 °C (99 °F). Multiple mutations are needed for the virus to grow at cold temperatures, so this process is effectively irreversible and once the virus has lost virulence (become "attenuated"), it will not regain the ability to infect people. To make the vaccine, the attenuated virus is grown in chicken eggs as before. The virus-containing fluid is harvested and the virus purified by filtration; this step also removes any contaminating bacteria. The filtered preparation is then diluted into a solution that stabilizes the virus. This solution contains monosodium glutamate, potassium phosphate, gelatin, the antibiotic gentamicin, and sugar.

A new method of producing influenza virus is used to produce the Novartis vaccine Optaflu. In this vaccine the virus is grown in cell culture instead of in eggs. This method is faster than the classic egg-based system and produces a purer final product. Importantly, there are no traces of egg proteins in the final product, so the vaccine is safe for people with egg allergies.

Previous seasonal vaccine production

The WHO recommended before the H1N1/09 outbreak that vaccines for the Northern Hemisphere's 2009–2010 flu season contain an A(H1N1)-like virus, and stocks have been made. However, the strain of H1N1 in the seasonal flu vaccine is different from the new pandemic strain H1N1/09 and offers no immunity against it. The US Centers for Disease Control and Prevention (CDC) characterized over 80 new H1N1 viruses that may be used in a vaccine.

Production questions and decisions

Questions

There was concern in mid-2009 that, should a second, deadlier wave of this new H1N1 strain appear during the Northern autumn of 2009, producing pandemic vaccines ahead of time could turn out to be a serious waste of resources as the vaccine might not be effective against it, and there would also be a shortage of seasonal flu vaccine available if production facilities were switched to the new vaccine. Seasonal flu vaccine was being made as of May 2009, according to *WebMD News*. The news site added that although vaccine makers would be ready to switch to making a swine flu vaccine, many questions remained unanswered, including: "Should we really make a swine flu vaccine? Should we base a vaccine on the current virus, since flu viruses change rapidly? Vaccine against the current virus might be far less effective against a changed virus - should we wait to see if the virus changes? If vaccine production doesn't start soon, swine flu vaccine won't be ready when it's needed."

The costs of producing a vaccine also became an issue, with some U.S. lawmakers questioning whether a new vaccine was worth the unknown benefits. Representatives Phil Gingrey and Paul Broun, for instance, were not convinced that the U.S. should spend up to USD\$2 billion to produce one, with Gingrey stating "We can't let all of our spending and our reaction be media-driven in responding to a panic so that we don't get Katrina-ed. ... It's important because what we are talking about as we discuss the appropriateness of spending \$2 billion to produce a vaccine that may never be used — that is a very important decision that our country has to make." In fact, a Fairleigh Dickinson University PublicMind poll found in October 2009 that a majority (62%) of New Jerseyans were not planning on getting the vaccine at all.

Before the pandemic was declared, the WHO said that if a pandemic was declared it would attempt to make sure that a substantial amount of vaccine was available for the benefit of developing countries. Vaccine makers and countries with standing orders, such as the U.S. and a number of European countries, would be asked, according to WHO officials, "to share with developing countries from the moment the first batches are ready if an H1N1 vaccine is made" for a pandemic strain. The global body stated that it wanted companies to donate at least 10 percent of their production or offer reduced prices for

poor countries that could otherwise be left without vaccines if there is a sudden surge in demand.

Gennady Onishchenko, Russia's chief doctor, said on June 2, 2009 that swine flu was not aggressive enough to cause a worldwide pandemic, noting that the current mortality rate of confirmed cases was 1.6% in Mexico and only 0.1% in the United States. He stated at a press conference, "So far it is unclear if we need to use vaccines against the flu because the virus that is now circulating throughout Europe and North America does not have a pandemic nature." In his opinion, a vaccine could be produced, but said that preparing a vaccine now would be considered "practice," since the world would soon need a new vaccine against a new virus. "What's 16,000 sick people? During any flu season, some 10,000 a day become ill in Moscow alone," he said.

Production timelines

After a meeting with the WHO on May 14, 2009, pharmaceutical companies said they were ready to begin making a swine flu vaccine. According to news reports, the WHO's experts will present recommendations to WHO Director-General Margaret Chan, who was expected to issue advice to vaccine manufacturers and the Sixty-second World Health Assembly. WHO's Keiji Fukuda told reporters "These are enormously complicated questions, and they are not something that anyone can make in a single meeting." Most flu vaccine companies can not make both seasonal flu vaccine and pandemic flu vaccine at the same time. Production takes months and it is impossible to switch halfway through if health officials make a mistake. If the swine flu mutates, scientists aren't sure how effective a vaccine made now from the current strain will remain. Rather than wait on the WHO decision, however, some countries in Europe have decided to go ahead with early vaccine orders.

On May 20, 2009, AP reported: "Manufacturers won't be able to start making the [swine flu] vaccine until mid-July at the earliest, weeks later than previous predictions, according to an expert panel convened by WHO. It will then take months to produce the vaccine in large quantities. The swine flu virus is not growing very fast in laboratories, making it difficult for scientists to get the key ingredient they need for a vaccine, the 'seed stock' from the virus [...] In any case, mass producing a pandemic vaccine would be a gamble, as it would take away manufacturing capacity for the seasonal flu vaccine for the flu that kills up to 500,000 people each year. Some experts have wondered whether the world really needs a vaccine for an illness that so far appears mild."

Another option proposed by the CDC was an "earlier rollout of seasonal vaccine," according to the CDC's Dr. Daniel Jernigan. He said the CDC would work with vaccine manufacturers and experts to see if that would be possible and desirable. Flu vaccination usually starts in September in the United States and peaks in November. Some vaccine experts agree it would be better to launch a second round of vaccinations against the new H1N1 strain instead of trying to add it to the seasonal flu vaccine or replacing one of its three components with the new H1N1 virus.

The Australian company CSL said that they were developing a vaccine for the swine flu and predicted that a suitable vaccine would be ready by August. However, John Sterling, Editor in Chief of *Genetic Engineering & Biotechnology News*, said on June 2, "It can take five or six months to come up with an entirely novel influenza vaccine. There is a great deal of hope that biotech and pharma companies might be able to have something ready sooner."

As of September 2009 a vaccine for H1N1/09 was expected to be available starting in November 2009, with production of three billion doses per year. It was expected that two doses would be needed to provide sufficient protection, but tests indicated that one dose would be sufficient for adults.

As of 28 September 2009 GlaxoSmithKline produced a vaccine made by growing the virus in hens' eggs, then breaking and deactivating the virus, and Baxter International produced a vaccine made in cell culture, suitable for those who have an egg allergy. The vaccines have been approved for use in the European Union.

Testing

Initial Phase I human testing began with Novartis' MF59 candidate in July 2009, at which time phase II trials of CSL's candidate CSL425 vaccine were planned to start in August 2009, but had not begun recruiting. Sanofi Pasteur's candidate inactivated H1N1 had several phase II trials planned as of 21 July 2009, but had not begun recruiting. News coverage conflicted with this information, as Australian trials of the CSL candidate were announced as having started on 21 July, and the Chinese government announce the start of trials of the Hualan Biological Engineering candidate.

Pandemrix, made by GlaxoSmithKline (GSK), and Focetria, made by Novartis were approved by the European Medicines Agency on 25 September 2009, and Celvapan, made by Baxter was approved the following week. The first comparative clinical study of both vaccines started on children in the United Kingdom on 25 September 2009. GSK announced results from clinical trials assessing the use of Pandemrix in children, adults, and the elderly. A 2009 trial examined the safety and efficacy of two different doses of the split-virus vaccine, and was published in the *New England Journal of Medicine*. The vaccine used in the trial was prepared by CSL Biotherapies in chicken eggs, in the same way as the seasonal vaccine. A robust immune response was produced in over 90% of patients after a single dose of either 15 or 30 µg of antigen. This study suggested that the current recommendation for two doses of vaccine are overkill and that a single dose is quite sufficient.

Arepanrix, an AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine similar to Pandemrix and also made by GSK, was authorized by Canada's Minister of Health on 21 October 2009.

Adverse events

A review by the U.S. National Institutes of Health (NIH) concluded that the 2009 H1N1 ("swine flu") vaccine has a safety profile similar to that of seasonal vaccine.

In an initial clinical trial in Australia, non-serious adverse events were reported by about half of the 240 people vaccinated, with these events including tenderness and pain at the site of injection, headache, malaise, and muscle pain. Two people had more severe events, with a much longer spell of nausea, muscle pain and malaise that lasted several days. The authors stated that the frequency and severity of these adverse events were similar to those normally seen with seasonal influenza vaccines. A second trial involved 2,200 people ranging from 3 to 77 years of age. In this study no patients reported serious adverse events, with the most commonly observed events being pain at the injection site and fever, which occurred in 10-25% of people. Although this trial followed up patients individually, the Government has been criticized for relying on voluntary reporting for post-vaccination evaluation in other circumstances, since this is "unlikely to accurately measure the percentage of people who get adverse effect".

As of 19 November 2009, the World Health Organization (WHO) said that 65 million doses of vaccine had been administered and that it had a similar safety profile to the seasonal flu vaccine, with no significant differences in the adverse events produced by the different types of vaccine. There has been one report of an adverse event per 10,000 doses of vaccine, with only five percent of these adverse events being serious, an overall rate of serious events of one in 200,000 doses.

In Canada, after 6.6 million doses of vaccine had been distributed between October 21 and November 7, there were reports of mild adverse events in 598 people vaccinated including: nausea, dizziness, headache, fever, vomiting, and swelling or soreness at the injection site. There were reports of tingling lips or tongue, difficulty breathing, hives, and skin rashes. Thirty six people had serious adverse events, including anaphylaxis and febrile convulsions. The rate of serious adverse events is one in 200,000 doses distributed, which according to Canada's chief public health officer, is less than expected for the seasonal flu vaccine. GlaxoSmithKline recalled a batch of vaccine in Canada after it appeared to cause higher rates of adverse events than other batches.

In the USA 46 million doses had been distributed as of 20 November 2009 and 3182 adverse events were reported. The CDC stated that the "vast majority" were mild, with about one serious adverse event in 260,000 doses.

In Japan around 15 million people had been vaccinated by 31 December 2009. 1,900 cases of side effects and 104 cases of death were reported from medical institutions. The health ministry announced that it will conduct epidemiologic investigation.

In France around five million people had been vaccinated by 30 December 2009. 2,657 cases of side effects, eight cases of intrauterine death and five cases of miscarriages were reported after vaccination by afssaps.

Rare potential adverse events are temporary bleeding disorders and Guillain-Barré syndrome (GBS), a serious condition involving the peripheral nervous system, from which most patients recover fully within a few months to a year. Some studies have indicated that influenza-like illness is itself associated with an increased risk of GBS, suggesting that vaccination might indirectly protect against the disorder by protecting against flu. According to Marie-Paule Kieny of WHO assessing the side-effects of large-scale influenza vaccination is complicated by the fact that in any large population a few people will become ill and die at any time. For example in any six-week period in the UK six sudden deaths from unknown causes and 22 cases of Guillain-Barré syndrome would be expected, so if everyone in the UK were vaccinated, this background rate of illness and death would continue as normal and some people would die simply by chance soon after the vaccination.

Some scientists have reported concerns about the longer-term effects of the vaccine. For instance, Sucharit Bhakdi, professor of medical microbiology at the Johannes Gutenberg University of Mainz in Germany, wrote in the journal, *Medical Microbiology and Immunology*, of the possibility that immune stimulation by vaccines or any other cause might worsen pre-existing heart disease. Chris Shaw, a neuroscientist at the University of British Columbia, expressed concern that serious side-effects may not appear immediately; he said it took five to ten years to see most of the Gulf War syndrome outcomes.

Pregnant women and children

A 2009 review of the use of influenza vaccines in pregnant women stated that influenza infections posed a major risk during pregnancy and that multiple studies had shown that the inactivated vaccine was safe in pregnant women, concluding that this vaccine "can be safely and effectively administered during any trimester of pregnancy" and that high levels of immunization would avert a "significant number of deaths". A 2004 review of the safety of influenza vaccines in children stated that the live vaccine had been shown to be safe but that it might trigger wheezing in some children with asthma; less data for the trivalent inactivated vaccine was available, but no serious symptoms had been seen in clinical trials.

Squalene

Newsweek states that "wild rumours" about the swine flu vaccine are being spread through e-mails, it writes that "The claims are nearly pure bunk, with only trace amounts of fact." These rumours generally make unfounded claims that the vaccine is dangerous and they may also promote conspiracy theories. For example, *Newsweek* states that some chain e-mails make false claims about squalene (shark liver oil) in vaccines. *The New York Times* also notes that anti-vaccine groups have spread "dire warnings" about formulations of the vaccine that contain squalene as an adjuvant. An adjuvant is a substance that boosts the body's immune response, thereby stretching the supply of the vaccine and helping immunize elderly people with a weak immune system. Squalene is a normal part of the human body, made in the liver and circulating in the blood, and is also

found in many foods, such as eggs and olive oil. None of the formulations of vaccine used in the US contain squalene, or any other adjuvant. However, some European and Canadian formulations do contain 25 µg of squalene per dose, which is roughly the amount found in a drop of olive oil. Some animal experiments have suggested that squalene might be linked to autoimmune disorders. although others suggest squalene might protect people against cancer.

Squalene-based adjuvants have been used in European influenza vaccines since 1997, with about 22 million doses administered over the past twelve years. The WHO states that no severe side effects have been associated with these vaccines, although they can produce mild inflammation at the site of injection. The safety of squalene-containing influenza vaccines have also been tested in two separate clinical trials, one with healthy non-elderly people, and one with elderly people, in both trials the vaccine was safe and well-tolerated, with only weak side-effects such as mild pain at the injection site. A 2009 meta-analysis brought together data from 64 clinical trials of influenza vaccines with the squalene-containing adjuvant MF59 and compared them to the effects of vaccines with no adjuvant. The analysis reported that the adjuvanted vaccines were associated with slightly lower risks of chronic diseases, but that neither type of vaccines altered the normal rate of autoimmune diseases; the authors concluded that their data "supports the good safety profile associated with MF59-adjuvanted influenza vaccines and suggests there may be a clinical benefit over non-MF59-containing vaccines". A 2004 review of the effects of adjuvants on mice and humans concluded that "despite numerous case reports on vaccination induced autoimmunity, most epidemiological studies failed to confirm the association and the risk appears to be extremely low or non-existent", although the authors noted that the possibility that adjuvants might cause damaging immune reactions in a few susceptible people has not been completely ruled out. A 2009 review of oil-based adjuvants in influenza vaccines stated that this type of adjuvant "neither stimulates antibodies against squalene oil naturally produced by the humans body nor enhances titers of preexisting antibodies to squalene" and that these formulations did not raise any safety concerns.

A paper published in 2000 suggested that squalene might have caused of Gulf War syndrome by producing anti-squalene antibodies, although other scientists stated that it was uncertain if the methods used were actually capable of detecting these antibodies. A 2009 U.S. Department of Defense study comparing healthy Navy personnel to those suffering from Gulf War syndrome was published in the journal *Vaccine*, this used a validated test for these antibodies and found no link between the presence of the antibodies and illness, with about half of both groups having these antibodies and no correlation between symptoms and antibodies. Furthermore, none of the vaccines given to US troops during the Gulf war actually contained any squalene adjuvants.

Thiomersal

Multi-dose versions of the vaccine contain the preservative thiomersal (also known as thimerosal), a mercury compound that prevents contamination when the vial is used repeatedly. Single-dose versions and the live vaccine do not contain this preservative. In

the U.S., one dose from a multi-dose vial contains approximately 25 micrograms of mercury, a bit less than a typical tuna fish sandwich. In Canada, different variants contain five and 50 micrograms of thimerosal per dose. The use of thiomersal has been controversial, with claims that it can cause autism and other developmental disorders. The U.S. Institute of Medicine examined these claims and concluded in 2004 that the evidence did not support any link between vaccines and autism. Other reviews came to similar conclusions, with a 2006 review in the *Canadian Journal of Neurological Sciences* stating that there is no convincing evidence to support the claim that thimerosal has a causal role in autism, and a 2009 review in the journal *Clinical Infectious Diseases* stating that claims that mercury can cause autism are "biologically implausible". The U.K. National Health Service stated in 2003 that "There is no evidence of long-term adverse effects due to the exposure levels of thiomersal in vaccines." The World Health Organization concluded that there is "no evidence of toxicity in infants, children or adults exposed to thiomersal in vaccines". Indeed, in 2008 a review noted that even though thiomersal was removed from all US childhood vaccines in 2001, this has not changed the number of autism diagnoses, which are still increasing.

Dystonia

According to the CDC, there is no evidence either for or against dystonia being caused by the vaccinations. Dystonia is extremely rare. Due to the very low numbers of cases, dystonia is poorly-understood. There were only five cases noted that might have been associated with influenza vaccinations over a span of eighteen years. In one recent case, a woman noted flu-like symptoms, followed by difficulties with movement and speech starting ten days after a seasonal influenza vaccination. However the Dystonia Medical Research Foundation stated that it is unlikely that the symptoms in this case were actually dystonia and stated that there has "never been a validated case of dystonia resulting from a flu shot".

Children Vaccine Recall

On December 15, 2009, One of the five manufacturers supplying the H1N1 vaccine to the United States recalled thousands of doses because they were not as potent as expected. The French manufacturer Sanofi Pasteur voluntarily recalled about 800,000 doses of vaccine meant for children between the ages of six months and 35 months. The company and the Centers for Disease Control and Prevention (CDC) emphasized that the recall was not prompted by safety concerns, and that even though the vaccine is not quite as potent as it is supposed to be, children who received it do not need to be immunized again. The CDC emphasized that there is no danger for any child who received the recalled vaccine. When asked what parents should do, CDC spokesman Tom Skinner said, "absolutely nothing." He said if children receive this vaccine, they will be fine.

Availability

Centers for Disease Control and Prevention



2,500 people line up in a mall in Texas City, Texas to receive the H1N1 vaccine from the Galveston County Health Department on October 30, 2009.

The American Centers for Disease Control and Prevention issued the following recommendations on who should be vaccinated (order is not in priority):

- Pregnant women, because they are at higher risk of complications and can potentially provide protection to infants who cannot be vaccinated;
- Household contacts and caregivers for children younger than 6 months of age, because younger infants are at higher risk of influenza-related complications and cannot be vaccinated. Vaccination of those in close contact with infants younger than 6 months old might help protect infants by "cocooning" them from the virus;
- Healthcare and emergency medical services personnel, because infections among healthcare workers have been reported and this can be a potential source of infection for vulnerable patients. Also, increased absenteeism in this population could reduce healthcare system capacity;
- All people from 6 months through 24 years of age:
 - Children from 6 months through 18 years of age, because cases of 2009 H1N1 influenza have been seen in children who are in close

contact with each other in school and day care settings, which increases the likelihood of disease spread, and

- Young adults 19 through 24 years of age, because many cases of 2009 H1N1 influenza have been seen in these healthy young adults and they often live, work, and study in close proximity, and they are a frequently mobile population; and,
- Persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza.
- Once the demand for these groups has been met at a local level, everyone from the ages of 25 through 64 years should be vaccinated too.

In addition, the CDC recommends

Children through 9 years of age should get two doses of vaccine, about a month apart. Older children and adults need only one dose.

National Health Service

Britain's National Health Service policy is to provide vaccine in this order of priority:

- People aged between six months and 65 years with:
 - chronic lung disease;
 - chronic heart disease;
 - chronic kidney disease;
 - chronic liver disease;
 - chronic neurological disease;
 - diabetes; or
 - suppressed immune system, whether due to disease or treatment.
- All pregnant women.
- People who live with someone whose immune system is compromised (for example, people with cancer or HIV/AIDS).
- People aged 65 and over in the seasonal flu vaccine at-risk groups.

This excludes the large majority of individuals aged six months to 24 years, a group for which the CDC recommends vaccination.

The NHS notes that:

- Healthy people over 65 years of age seem to have some natural immunity.
- Children, while disproportionately affected, tend to make full recoveries.
- The vaccine is ineffective in young infants.

The United Kingdom began its administration program October 21, 2009. UK Soldiers serving in Afghanistan will also be offered vaccination.

Surplus vaccine

By April 2010, it was apparent that most of the vaccine was not needed. The US government had bought 229 million doses of H1N1 vaccines of which 91 million doses were used; of the surplus, some of it was stored in bulk, some of it was sent to developing countries and 71 million doses will be destroyed. The World Health Organization is planning to examine if it overreacted to the H1N1 outbreak.

Political issues



US President Barack Obama receives the vaccine on December 20, 2009

General political issues, not restricted to the 2009 outbreak, arose regarding the distribution of vaccine. In many countries supplies are controlled by national or local governments, and the question of how the vaccine will be allocated should there be an insufficient supply for everyone is critical, and will likely depend on the patterns of any pandemic, and the age groups most at risk for serious complications, including death. In the case of a lethal pandemic people will be demanding access to the vaccine and the major problem will be making it available to those who need it.

While it has been suggested that compulsory vaccination may be needed to control a pandemic, many countries do not have a legal framework that would allow this. The only populations easily compelled to accept vaccination are military personnel (who can be given routine vaccinations as part of their service obligations), health care personnel (who can be required to be vaccinated to protect patients), and school children, who (under United States constitutional law) could be required to be vaccinated as a condition of attending school.

In August 2010, the *Daily Mail* printed an article that stated that "a third of the experts advising the World Health Organisation about the swine flu pandemic had ties to drugs firms" and that of the 20 members of the Scientific Advisory Group for Emergencies, which advised the British Government on swine flu, 11 had done work for the pharmaceutical industry or were linked to it through their universities. A spokesman for the WHO is stated as having "denied that the experts' work gave rise to a conflict of interest".

Chapter 7

Avian Influenza

Avian influenza, sometimes **avian flu**, and commonly **bird flu**, refers to "influenza caused by viruses adapted to birds." Of the greatest concern is **highly pathogenic avian influenza (HPAI)**.

"Bird flu" is a phrase similar to "swine flu," "dog flu," "horse flu," or "human flu" in that it refers to an illness caused by any of many different strains of influenza viruses that have adapted to a specific host. All known viruses that cause influenza in birds belong to the species *influenza A virus*. All subtypes (but not all strains of all subtypes) of influenza A virus are adapted to birds, which is why for many purposes avian flu virus *is* the influenza A virus (note that the "A" does *not* stand for "avian").

Adaptation is non-exclusive. Being adapted towards a particular species does not preclude adaptations, or partial adaptations, towards infecting different species. In this way strains of influenza viruses are adapted to multiple species, though may be preferential towards a particular host. For example, viruses responsible for influenza pandemics are adapted to both humans and birds. Recent influenza research into the genes of the Spanish flu virus shows it to have genes adapted to both birds and humans; with more of its genes from birds than less deadly later pandemic strains.

Genetics

Genetic factors in distinguishing between "human flu viruses" and "avian flu viruses" include:

PB2: (RNA polymerase): Amino acid (or residue) position 627 in the PB2 protein encoded by the PB2 RNA gene. Until H5N1, all known avian influenza viruses had a Glu at position 627, while all human influenza viruses had a Lys.

HA: (hemagglutinin): Avian influenza HA bind alpha 2-3 sialic acid receptors while human influenza HA bind alpha 2-6 sialic acid receptors. Swine influenza viruses have the ability to bind both types of sialic acid receptors. Hemagglutinin is the major antigen of the virus against which neutralizing antibodies are produced and influenza virus epidemics are associated with changes in its antigenic structure. This was originally derived from pigs, and should technically be referred to as "Pig Flu"

Subtypes

There are many subtypes of avian influenza viruses, but only some strains of four subtypes have been highly pathogenic in humans. These are types H5N1, H7N3, H7N7 and H9N2.

Contraction/Spreading of Avian Influenza

Most human contractions of the Avian flu are a result of either handling dead infected birds or from contact with infected fluids. While most wild birds mainly have only a mild form of the H5N1 strain, once domesticated birds such as chickens or turkeys are infected, it could become much more deadly due to the fact that the birds are often within close contact of one another. There is currently a large threat of this in Asia with infected poultry due to low hygiene conditions and close quarters. Although it is easy for humans to become infected from birds, it's much more difficult to do so from human to human without close and lasting contact.

Spreading of H5N1 from Asia to Europe is much more likely the cause of both legal and illegal poultry trades than dispersing through wild bird migrations, being that in recent studies, there were no secondary rises in infection in Asia when wild birds migrate south again from their breeding grounds. Instead, the infection patterns followed transportation such as railroads, roads, and Country borders, suggesting poultry trade as being much more likely. While there have been strains of Avian Flu to exist in the United States, such as Texas in 2004, they have been extinguished and have not been known to infect humans.

Examples of avian influenza A virus strains:

HA subtype designation	NA subtype designation	Avian influenza A viruses
H1	N1	A/duck/Alberta/35/76(H1N1)
H1	N8	A/duck/Alberta/97/77(H1N8)
H2	N9	A/duck/Germany/1/72(H2N9)
H3	N8	A/duck/Ukraine/63(H3N8)
H3	N8	A/duck/England/62(H3N8)
H3	N2	A/turkey/England/69(H3N2)
H4	N6	A/duck/Czechoslovakia/56(H4N6)
H4	N3	A/duck/Alberta/300/77(H4N3)
H5	N3	A/tern/South Africa/300/77(H4N3)
H5	N4	A/jyotichinara/Ethiopia/300/77(H6N6)
H5	N9	A/turkey/Ontario/7732/66(H5N9)

H5	N1	A/chick/Scotland/59(H5N1)
H6	N2	A/turkey/Massachusetts/3740/65(H6N2)
H6	N8	A/turkey/Canada/63(H6N8)
H6	N5	A/shearwater/Australia/72(H6N5)
H6	N1	A/duck/Germany/1868/68(H6N1)
H7	N7	A/fowl plague virus/Dutch/27(H7N7)
H7	N1	A/chick/Brescia/1902(H7N1)
H7	N3	A/turkey/England/639H7N3)
H7	N1	A/fowl plague virus/Rostock/34(H7N1)
H8	N4	A/turkey/Ontario/6118/68(H8N4)
H9	N2	A/turkey/Wisconsin/1/66(H9N2)
H9	N6	A/duck/Hong Kong/147/77(H9N6)
H9	N6	A/duck/Hong Kong/147/77(H9N6)
H9	N8	A/manishsurpur/Malawi/149/77(H9N8)
H9	N7	A/turkey/Scotland/70(H9N7)
H10	N8	A/quail/Italy/1117/65(H10N8)
H11	N6	A/duck/England/56(H11N6)
H11	N9	A/duck/Memphis/546/74(H11N9)
H12	N5	A/duck/Alberta/60/76/(H12N5)
H13	N6	A/gull/Maryland/704/77(H13N6)
H14	N4	A/duck/Gurjev/263/83(H14N4)
H15	N9	A/shearwater/Australia/2576/83(H15N9)

Influenza pandemic

Pandemic flu viruses have some avian flu virus genes and usually some human flu virus genes. Both the H2N2 and H3N2 pandemic strains contained genes from avian influenza viruses. The new subtypes arose in pigs coinfecting with avian and human viruses and were soon transferred to humans. Swine were considered the original "intermediate host" for influenza, because they supported reassortment of divergent subtypes. However, other hosts appear capable of similar coinfection (e.g., many poultry species), and direct transmission of avian viruses to humans is possible. The Spanish flu virus strain may have been transmitted directly from birds to humans. In spite of their pandemic connection, avian influenza viruses are noninfectious for most species. When they are infectious they are usually asymptomatic, so the carrier does not have any disease from it. Thus while infected with an avian flu virus, the animal doesn't have a "flu". Typically, when illness (called "flu") from an avian flu virus *does* occur, it is the result of an avian flu virus strain adapted to one species spreading to another species (usually from one bird species to another bird species). So far as is known, the most common result of this is an

illness so minor as to be not worth noticing (and thus little studied). But with the domestication of chickens and turkeys, humans have created species subtypes (domesticated poultry) that can catch an avian flu virus adapted to waterfowl and have it rapidly mutate into a form that kills in days over 90% of an entire flock and spread to other flocks and kill 90% of *them* and can only be stopped by killing every domestic bird in the area. Until H5N1 infected humans in the 1990s, this was the only reason avian flu was considered important. Since then, avian flu viruses have been intensively studied; resulting in changes in what is believed about flu pandemics, changes in poultry farming, changes in flu vaccination research, and changes in flu pandemic planning.

H5N1 has evolved into a flu virus strain that infects more species than any previously known flu virus strain, is deadlier than any previously known flu virus strain, and continues to evolve becoming both more widespread and more deadly causing Robert G. Webster, a leading expert on avian flu, to publish an article titled "The world is teetering on the edge of a pandemic that could kill a large fraction of the human population" in *American Scientist*. He called for adequate resources to fight what he sees as a major world threat to possibly billions of lives. Since the article was written, the world community has spent billions of dollars fighting this threat with limited success.

Vaccines have been formulated against several of the avian H5N1 influenza varieties. Vaccination of poultry against the ongoing H5N1 epizootic is widespread in certain countries. Some vaccines also exist for use in humans, and others are in testing, but none have been made available to civilian populations, nor produced in quantities sufficient to protect more than a tiny fraction of the Earth's population in the event that an H5N1 pandemic breaks out. The World Health Organization has compiled a list of known clinical trials of pandemic influenza prototype vaccines, including those against H5N1.

H5N1



The highly pathogenic influenza A virus subtype H5N1 virus is an emerging avian influenza virus that has been causing global concern as a potential pandemic threat. It is often referred to simply as "bird flu" or "avian influenza" even though it is only one subtype of avian influenza causing virus.

H5N1 has killed millions of poultry in a growing number of countries throughout Asia, Europe and Africa. Health experts are concerned that the co-existence of human flu viruses and avian flu viruses (especially H5N1) will provide an opportunity for genetic material to be exchanged between species-specific viruses, possibly creating a new virulent influenza strain that is easily transmissible and lethal to humans.

Since the first H5N1 outbreak occurred in 1987, there has been an increasing number of HPAI H5N1 bird-to-human transmissions leading to clinically severe and fatal human infections. However, because there is a significant species barrier that exists between birds and humans, the virus does not easily cross over to humans, though some cases of infection are being researched to discern whether human to human transmission is occurring. More research is necessary to understand the pathogenesis and epidemiology of the H5N1 virus in humans. Exposure routes and other disease transmission characteristics such as genetic and immunological factors, that may increase the likelihood of infection, are not clearly understood.

On January 18, 2009, a 27-year-old woman from eastern China died of bird flu, Chinese authorities said, making her the second person to die from the deadly virus at that time. Two tests on the woman were positive for H5N1 avian influenza, said the ministry, which did not say how she might have contracted the virus.

Although millions of birds have become infected with the virus since its discovery, 302 humans have died from the H5N1 in twelve countries according to WHO data as of November 19, 2010.

The avian flu claimed at least 300 humans in Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Laos, Nigeria, Pakistan, Thailand, Turkey, and Vietnam. Epidemiologists are afraid that the next time such a virus mutates, it could pass from human to human; however, the current A/H5N1 virus does not transmit easily from human to human. If this form of transmission occurs, another pandemic could result. Thus disease-control centers around the world are making avian flu a top priority. These organizations encourage poultry-related operations to develop a preemptive plan to prevent the spread of H5N1 and its potentially pandemic strains. The recommended plans center on providing protective clothing for workers and isolating flocks to prevent the spread of the virus.

The Thailand outbreak of avian flu caused massive economic losses especially among poultry workers. Infected birds were culled and sacrificed. The public lost confidence with the poultry products, thus decreasing the consumption of chicken products. This also elicited a ban from importing countries. There were however, factors which aggravated the spread of the virus which includes bird migration, cool temperature (increases virus survival) and several festivals at that time.

In domestic animals

Several domestic species have been infected with and shown symptoms of H5N1 viral infection including cats, dogs, ferrets, pigs, and birds.

Birds

Attempts are made in the United States not to minimize the presence of highly pathogenic avian influenza (HPAI) in poultry in thorough routine surveillance of poultry flocks in commercial poultry operations. Detection of a HPAI virus may result in immediate culling of the flock. Less pathogenic viruses are controlled by vaccination, which is done primarily in turkey flocks (ATCvet codes: QI01AA23 for the inactivated fowl vaccine, QI01CL01 for the inactivated turkey combination vaccine).

Chapter 8

Influenza A Virus

Influenza A virus causes influenza in birds and some mammals and is the only species of Influenzavirus A. Influenzavirus A is a genus of the Orthomyxoviridae family of viruses. Strains of all subtypes of influenza A virus have been isolated from wild birds, although disease is uncommon. Some isolates of influenza A virus cause severe disease both in domestic poultry and, rarely, in humans. Occasionally viruses are transmitted from wild aquatic birds to domestic poultry and this may cause an outbreak or give rise to human influenza pandemics.

Influenza A viruses are negative sense, single-stranded, segmented RNA viruses. There are several subtypes, labeled according to an H number (for the type of hemagglutinin) and an N number (for the type of neuraminidase). There are 16 different H antigens (H1 to H16) and nine different N antigens (N1 to N9). The newest H type (H16) was isolated from Black-headed Gulls caught in Sweden and the Netherlands in 1999 and reported in the literature in 2005.

Each virus subtype has mutated into a variety of strains with differing pathogenic profiles; some pathogenic to one species but not others, some pathogenic to multiple species.

A filtered and purified Influenza A vaccine for humans was developed and many countries have stockpiled it to allow a quick administration to the population in the event of an Avian influenza pandemic. Avian influenza is sometimes called avian flu, and commonly bird flu.

Variants and subtypes

Some Variants are identified and named according to the isolate that they are like and thus are presumed to share lineage (example Fujian flu virus like); according to their typical host (example Human flu virus); according to their subtype (example H3N2); and according to their deadliness (example LP, Low Pathogenic). So a flu from a virus similar to the isolate A/Fujian/411/2002(H3N2) is called Fujian flu, human flu, and H3N2 flu.

Variants are sometimes named according to the species (host) the strain is endemic in or adapted to. The main variants named using this convention are:

- Bird flu
- Human flu
- Swine influenza
- Equine influenza
- Canine influenza

Variants have also sometimes been named according to their deadliness in poultry, especially chickens:

- Low Pathogenic Avian Influenza (LPAI)
- Highly Pathogenic Avian Influenza (HPAI), also called: deadly flu or death flu

Most known strains are extinct strains. For example, the annual flu subtype H3N2 no longer contains the strain that caused the Hong Kong flu.

Annual flu

The annual flu (also called "seasonal flu" or "human flu") in the U.S. "results in approximately 36,000 deaths and more than 200,000 hospitalizations each year. In addition to this human toll, influenza is annually responsible for a total cost of over \$10 billion in the U.S."

The annually updated trivalent influenza vaccine consists of hemagglutinin (HA) surface glycoprotein components from influenza H3N2, H1N1, and B influenza viruses.

Measured resistance to the standard antiviral drugs amantadine and rimantadine in H3N2 has increased from 1% in 1994 to 12% in 2003 to 91% in 2005.

"[C]ontemporary human H3N2 influenza viruses are now endemic in pigs in southern China and can reassort with avian H5N1 viruses in this intermediate host."

Structure and genetics

"The physical structure of all influenza A viruses is similar. The virions or virus particles are enveloped and can be either spherical or filamentous in form. In clinical isolates that have undergone limited passages in eggs or tissue culture, there are more filamentous than spherical particles, whereas passaged laboratory strains consist mainly of spherical virions."

The Influenza A virus genome is contained on eight single (non-paired) RNA strands that code for eleven proteins (HA, NA, NP, M1, M2, NS1, NEP, PA, PB1, PB1-F2, PB2). The total genome size is 13,588 bases. The segmented nature of the genome allows for the exchange of entire genes between different viral strains during cellular cohabitation. The eight RNA segments are:

- HA encodes hemagglutinin (about 500 molecules of hemagglutinin are needed to make one virion) "The extent of infection into host organism is determined by HA. Influenza viruses bud from the apical surface of polarized epithelial cells (e.g. bronchial epithelial cells) into lumen of lungs and are therefore usually pneumotropic. The reason is that HA is cleaved by trypsin which is restricted to lungs. However HAs of H5 and H7 pantropic avian viruses subtypes can be cleaved by furin and subtilisin-type enzymes, allowing the virus to grow in other organs than lungs."
- NA encodes neuraminidase (about 100 molecules of neuraminidase are needed to make one virion).
- NP encodes nucleoprotein.
- M encodes two matrix proteins (the M1 and the M2) by using different reading frames from the same RNA segment (about 3000 matrix protein molecules are needed to make one virion).
- NS encodes two distinct non-structural proteins (NS1 and NEP) by using different reading frames from the same RNA segment.
- PA encodes an RNA polymerase.
- PB1 encodes an RNA polymerase and PB1-F2 protein (induces apoptosis) by using different reading frames from the same RNA segment.
- PB2 encodes an RNA polymerase.

The genome segments have common terminal sequences, and the ends of the RNA strands are partially complementary, allowing them to bond to each other by hydrogen bonds. After transcription from negative-sense to positive-sense RNA the +RNA strands get the cellular 5' cap added by cap snatching, which involves the viral protein NS1 binding to the cellular pre-mRNAs. The cap is then cleaved from the cellular pre-mRNA using a second viral protein, PB2. The short oligo cap is then added to the influenza +RNA strands, allowing its processing as messenger RNA by ribosomes. The +RNA strands also serve for synthesis of -RNA strands for new virions.

The RNA synthesis and its assembly with the nucleoprotein takes place in the cell nucleus, the synthesis of proteins takes place in the cytoplasm. The assembled virion cores leave the nucleus and migrate towards the cell membrane, with patches of viral transmembrane proteins (hemagglutinin, neuraminidase and M2 proteins) and an underlying layer of the M1 protein, and bud through these patches, releasing finished enveloped viruses into the extracellular fluid.

In nonhumans

Avian influenza

Fowl act as natural asymptomatic carriers of Influenza A viruses. Prior to the current H5N1 epizootic, strains of Influenza A virus had been demonstrated to be transmitted from wild fowl to only birds, pigs, horses, seals, whales and humans; and only between humans and pigs and between humans and domestic fowl; and not other pathways such as domestic fowl to horse.

Wild aquatic birds are the natural hosts for a large variety of influenza A viruses. Occasionally viruses are transmitted from these birds to other species and may then cause devastating outbreaks in domestic poultry or give rise to human influenza pandemics.

H5N1 has been shown to be transmitted to tigers, leopards, and domestic cats that were fed uncooked domestic fowl (chickens) with the virus. H3N8 viruses from horses have crossed over and caused outbreaks in dogs. Laboratory mice have been infected successfully with a variety of avian flu genotypes.

Influenza A viruses spread in the air and in manure and survives longer in cold weather. It can also be transmitted by contaminated feed, water, equipment and clothing; however, there is no evidence that the virus can survive in well-cooked meat. Symptoms in animals vary, but virulent strains can cause death within a few days.

"Highly pathogenic avian influenza virus is on every top ten list available for potential agricultural bioweapon agents".

Avian influenza viruses that the OIE and others test for in order to control poultry disease include: H5N1, H7N2, H1N7, H7N3, H13N6, H5N9, H11N6, H3N8, H9N2, H5N2, H4N8, H10N7, H2N2, H8N4, H14N5, H6N5, H12N5 and others.

Known outbreaks of highly pathogenic flu in poultry 1959-2003

Year	Area	Affected	Subtype
1959	Scotland	chicken	H5N1
1963	England	turkey	H7N3
1966	Ontario (Canada)	turkey	H5N9
1976	Victoria (Australia)	chicken	H7N7
1979	Germany	chicken	H7N7
1979	England	turkey	H7N7
1983	Pennsylvania (USA)*	chicken, turkey	H5N2
1983	Ireland	turkey	H5N8
1985	Victoria (Australia)	chicken	H7N7
1991	England	turkey	H5N1
1992	Victoria (Australia)	chicken	H7N3
1994	Queensland (Australia)	chicken	H7N3
1994	Mexico*	chicken	H5N2
1994	Pakistan*	chicken	H7N3
1997	New South Wales (Australia)	chicken	H7N4
1997	Hong Kong (China)*	chicken	H5N1
1997	Italy	chicken	H5N2
1999	Italy*	turkey	H7N1
2002	Hong Kong (China)	chicken	H5N1

2002	Chile	chicken	H7N3
2003	Netherlands*	chicken	H7N7

**Outbreaks with significant spread to numerous farms, resulting in great economic losses. Most other outbreaks involved little or no spread from the initially infected farms.*

1979: "More than 400 harbor seals, most of them immature, died along the New England coast between December 1979 and October 1980 of acute pneumonia associated with influenza virus, A/Seal/Mass/1/180 (H7N7)."

1995: "[V]accinated birds can develop asymptomatic infections that allow virus to spread, mutate, and recombine (ProMED-mail, 2004j). Intensive surveillance is required to detect these "silent epidemics" in time to curtail them. In Mexico, for example, mass vaccination of chickens against epidemic H5N2 influenza in 1995 has had to continue in order to control a persistent and evolving virus (Lee et al., 2004)."

1997: "Influenza A viruses normally seen in one species sometimes can cross over and cause illness in another species. For example, until 1997, only H1N1 viruses circulated widely in the U.S. pig population. However, in 1997, H3N2 viruses from humans were introduced into the pig population and caused widespread disease among pigs. Most recently, H3N8 viruses from horses have crossed over and caused outbreaks in dogs."

2000: "In California, poultry producers kept their knowledge of a recent H6N2 avian influenza outbreak to themselves due to their fear of public rejection of poultry products; meanwhile, the disease spread across the western United States and has since become endemic."

2003: In Netherlands H7N7 influenza virus infection broke out in poultry on several farms.

2004: In North America, the presence of avian influenza strain H7N3 was confirmed at several poultry farms in British Columbia in February 2004. As of April 2004, 18 farms had been quarantined to halt the spread of the virus.

2005: Tens of millions of birds died of H5N1 influenza and hundreds of millions of birds were culled to protect humans from H5N1. H5N1 is endemic in birds in southeast Asia and represents a long term pandemic threat.

2006: H5N1 spreads across the globe killing hundreds of millions of birds and over 100 people causing a significant H5N1 impact from both actual deaths and predicted possible deaths.

Swine flu

Swine influenza (or "pig influenza") refers to a subset of Orthomyxoviridae that create influenza in pigs and are endemic in pigs. The species of Orthomyxoviridae that can cause flu in pigs are Influenza A virus and Influenza C virus but not all genotypes of these two species infect pigs. The known subtypes of Influenza A

virus that create influenza in pigs and are endemic in pigs are H1N1, H1N2, H3N1 and H3N2.

Horse flu

Horse flu (or "Equine influenza") refers to varieties of Influenza A virus that affect horses. Horse 'flu viruses were only isolated in 1956. There are two main types of virus called equine-1 (H7N7) which commonly affects horse heart muscle and equine-2 (H3N8) which is usually more severe.

Dog flu

Dog flu (or "canine influenza") refers to varieties of Influenza A virus that affect dogs. The equine influenza virus H3N8 was found to infect and kill - with respiratory illness - greyhound race dogs at a Florida racetrack in January 2004.

H3N8

H3N8 is now endemic in birds, horses and dogs.

Human influenza virus



Japanese commuter wearing a face mask

"Human influenza virus" usually refers to those subtypes that spread widely among humans. H1N1, H1N2, and H3N2 are the only known Influenza A virus subtypes currently circulating among humans.

Genetic factors in distinguishing between "human flu viruses" and "avian influenza viruses" include:

PB2: (RNA polymerase): Amino acid (or residue) position 627 in the PB2 protein encoded by the PB2 RNA gene. Until H5N1, all known avian influenza viruses had a Glu at position 627, while all human influenza viruses had a lysine.

HA: (hemagglutinin): Avian influenza HA bind alpha 2-3 sialic acid receptors while human influenza HA bind alpha 2-6 sialic acid receptors. Swine influenza viruses have the ability to bind both types of sialic acid receptors.

"About 52 key genetic changes distinguish avian influenza strains from those that spread easily among people, according to researchers in Taiwan, who analyzed the genes of more than 400 A type flu viruses." "How many mutations would make an avian virus capable of infecting humans efficiently, or how many mutations would render an influenza virus a pandemic strain, is difficult to predict. We have examined sequences from the 1918 strain, which is the only pandemic influenza virus that could be entirely derived from avian strains. Of the 52 species-associated positions, 16 have residues typical for human strains; the others remained as avian signatures. The result supports the hypothesis that the 1918 pandemic virus is more closely related to the avian influenza A virus than are other human influenza viruses."

Human flu symptoms usually include fever, cough, sore throat, muscle aches, conjunctivitis and, in severe cases, severe breathing problems and pneumonia that may be fatal. The severity of the infection will depend to a large part on the state of the infected person's immune system and if the victim has been exposed to the strain before, and is therefore partially immune.

Highly pathogenic H5N1 avian influenza in a human is far worse, killing 50% of humans that catch it. In one case, a boy with H5N1 experienced diarrhea followed rapidly by a coma without developing respiratory or flu-like symptoms.

The Influenza A virus subtypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:

- H1N1 caused "Spanish Flu" and the 2009 swine flu outbreak
- H2N2 caused "Asian Flu" in the late 1950s
- H3N2 caused "Hong Kong Flu" in the late 1960s
- H5N1 considered a global influenza pandemic threat through its spread in the mid-2000s
- H7N7 has unusual zoonotic potential
- H1N2 is currently endemic in humans and pigs
- H9N2, H7N2, H7N3, H5N2, H10N7.

H1N1

H1N1 is currently pandemic in both human and pig populations. A variant of H1N1 was responsible for the Spanish flu pandemic that killed some 50 million to 100 million people worldwide over about a year in 1918 and 1919. Another variant was named a pandemic threat in the 2009 flu pandemic. Controversy arose

in October, 2005, after the H1N1 genome was published in the journal, *Science*, because of fears that this information could be used for bioterrorism.

H2N2

The Asian Flu was a pandemic outbreak of H2N2 avian influenza that originated in China in 1957, spread worldwide that same year during which a influenza vaccine was developed, lasted until 1958 and caused between one and four million deaths.

H3N2

H3N2 is currently endemic in both human and pig populations. It evolved from H2N2 by antigenic shift and caused the Hong Kong Flu pandemic of 1968 and 1969 that killed up to 750,000. "An early-onset, severe form of influenza A H3N2 made headlines when it claimed the lives of several children in the United States in late 2003."

The dominant strain of annual flu in January 2006 is H3N2. Measured resistance to the standard antiviral drugs amantadine and rimantadine in H3N2 has increased from 1% in 1994 to 12% in 2003 to 91% in 2005.

"[C]ontemporary human H3N2 influenza viruses are now endemic in pigs in southern China and can reassort with avian H5N1 viruses in this intermediate host."

H5N1

H5N1 is the world's major influenza pandemic threat.

"When he compared the 1918 virus with today's human flu viruses, Dr.

Taubenberger noticed that it had alterations in just 25 to 30 of the virus's 4,400 amino acids. Those few changes turned a bird virus into a killer that could spread from person to person."

H7N7

H7N7 has unusual zoonotic potential. In 2003 in Netherlands 89 people were confirmed to have H7N7 influenza virus infection following an outbreak in poultry on several farms. One death was recorded.

H1N2

H1N2 is currently endemic in both human and pig populations. The new H1N2 strain appears to have resulted from the reassortment of the genes of the currently circulating influenza H1N1 and H3N2 subtypes. The hemagglutinin protein of the H1N2 virus is similar to that of the currently circulating H1N1 viruses and the neuraminidase protein is similar to that of the current H3N2 viruses.

H9N2

Low pathogenic avian influenza A (H9N2) infection was confirmed in 1999, in China and Hong Kong in two children, and in 2003 in Hong Kong in one child. All three fully recovered.

H7N2

One person in New York in 2003 and one person in Virginia in 2002 were found to have serologic evidence of infection with H7N2. Both fully recovered.

H7N3

In North America, the presence of avian influenza strain H7N3 was confirmed at several poultry farms in British Columbia in February 2004. As of April 2004, 18 farms had been quarantined to halt the spread of the virus. Two cases of humans

with avian influenza have been confirmed in that region. "Symptoms included conjunctivitis and mild influenza-like illness." Both fully recovered.

H5N2

Japan's Health Ministry said January 2006 that poultry farm workers in Ibaraki prefecture may have been exposed to H5N2 in 2005. The H5N2 antibody titers of paired sera of 13 subjects increased fourfold or more.

H10N7

In 2004 in Egypt H10N7 was reported for the first time in humans. It caused illness in two infants in Egypt. One child's father is a poultry merchant.

Evolution

Taubenberger says:

"All influenza A pandemics since [the Spanish flu pandemic], and indeed almost all cases of influenza A worldwide (excepting human infections from avian viruses such as H5N1 and H7N7), have been caused by descendants of the 1918 virus, including "drifted" H1N1 viruses and reassorted H2N2 and H3N2 viruses. The latter are composed of key genes from the 1918 virus, updated by subsequently incorporated avian influenza genes that code for novel surface proteins, making the 1918 virus indeed the "mother" of all pandemics.

Researchers from the National Institutes of Health used data from the Influenza Genome Sequencing Project and concluded that during the ten-year period examined most of the time the hemagglutinin gene in H3N2 showed no significant excess of mutations in the antigenic regions while an increasing variety of strains accumulated. This resulted in one of the variants eventually achieving higher fitness, becoming dominant, and in a brief interval of rapid evolution rapidly sweeping through the population and eliminating most other variants.

Chapter 9

Influenza A Virus Subtype H5N1

Influenza A virus subtype H5N1, also known as "**bird flu**", **A(H5N1)** or simply **H5N1**, is a subtype of the Influenza A virus which can cause illness in humans and many other animal species. A bird-adapted strain of H5N1, called **HPAI A(H5N1)** for "highly pathogenic avian influenza virus of type A of subtype H5N1", is the causative agent of H5N1 flu, commonly known as "avian influenza" or "bird flu". It is enzootic in many bird populations, especially in Southeast Asia. One strain of HPAI A(H5N1) is spreading globally after first appearing in Asia. It is epizootic (an epidemic in nonhumans) and panzootic (affecting animals of many species, especially over a wide area), killing tens of millions of birds and spurring the culling of hundreds of millions of others to stem its spread. Most references to "bird flu" and H5N1 in the popular media refer to this strain.

According to the FAO Avian Influenza Disease Emergency Situation Update, H5N1 pathogenicity is continuing to gradually rise in endemic areas but the avian influenza disease situation in farmed birds is being held in check by vaccination. Eleven outbreaks of H5N1 were reported worldwide in June 2008 in five countries (China, Egypt, Indonesia, Pakistan and Vietnam) compared to 65 outbreaks in June 2006 and 55 in June 2007. The "global HPAI situation can be said to have improved markedly in the first half of 2008 [but] cases of HPAI are still underestimated and underreported in many countries because of limitations in country disease surveillance systems". On December 9, 2010 the WHO announced a total of 510 human cases which resulted in the deaths of 303 people since 2003.

A filtered and purified Influenza A vaccine for humans is being developed and many countries have recommended it be stockpiled so, if an Avian influenza pandemic starts jumping to humans, the vaccine can quickly be administered to avoid loss of life. Avian influenza is sometimes called avian flu, and commonly bird flu.

Overview

HPAI A(H5N1) is considered an avian disease, although there is some evidence of limited human-to-human transmission of the virus. A risk factor for contracting the virus is handling of infected poultry, but transmission of the virus from infected birds to humans is inefficient. Still, around 60% of humans known to have been infected with the current Asian strain of HPAI A(H5N1) have died from it, and H5N1 may mutate or

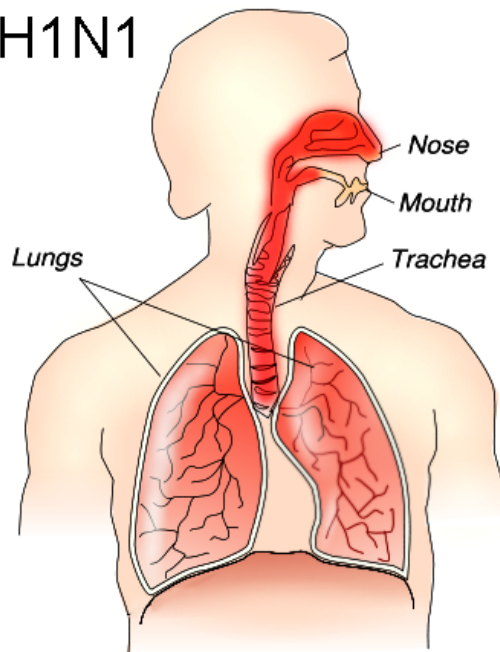
reassort into a strain capable of efficient human-to-human transmission. In 2003, world-renowned virologist Robert G. Webster published an article titled "The world is teetering on the edge of a pandemic that could kill a large fraction of the human population" in *American Scientist*. He called for adequate resources to fight what he sees as a major world threat to possibly billions of lives. On September 29, 2005, David Nabarro, the newly appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill anywhere between 5 million and 150 million people. Experts have identified key events (creating new clades, infecting new species, spreading to new areas) marking the progression of an avian flu virus towards becoming pandemic, and many of those key events have occurred more rapidly than expected.

Due to the high lethality and virulence of HPAI A(H5N1), its endemic presence, its increasingly large host reservoir, and its significant ongoing mutations, the H5N1 virus is the world's largest current pandemic threat and billions of dollars are being spent researching H5N1 and preparing for a potential influenza pandemic. At least 12 companies and 17 governments are developing pre-pandemic influenza vaccines in 28 different clinical trials that, if successful, could turn a deadly pandemic infection into a nondeadly one. Full-scale production of a vaccine that could prevent any illness at all from the strain would require at least three months after the virus's emergence to begin, but it is hoped that vaccine production could increase until one billion doses were produced by one year after the initial identification of the virus.

H5N1 may cause more than one influenza pandemic as it is expected to continue mutating in birds regardless of whether humans develop herd immunity to a future pandemic strain. Influenza pandemics from its genetic offspring may include influenza A virus subtypes other than H5N1. While genetic analysis of the H5N1 virus shows that influenza pandemics from its genetic offspring can easily be far more lethal than the Spanish flu pandemic, planning for a future influenza pandemic is based on what can be done and there is no higher Pandemic Severity Index level than a Category 5 pandemic which, roughly speaking, is any pandemic as bad as the Spanish flu or worse; and for which *all* intervention measures are to be used.

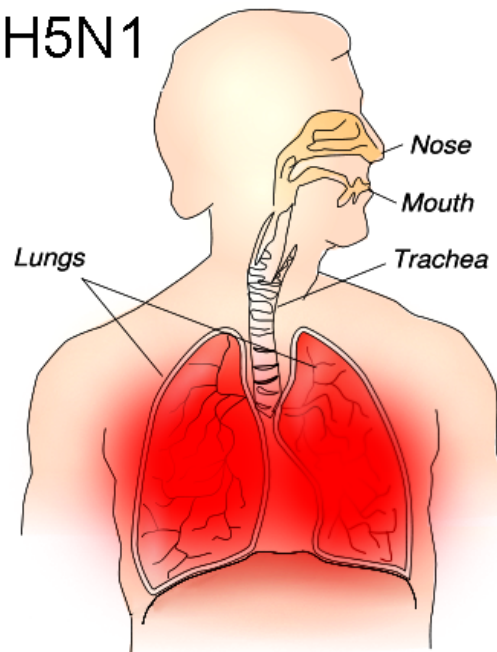
Signs and symptoms

H1N1



Easily spread
Rarely fatal

H5N1



Spreads slowly
Often fatal

The different sites of infection (shown in red) of seasonal H1N1 versus avian H5N1. This influences their lethality and ability to spread.

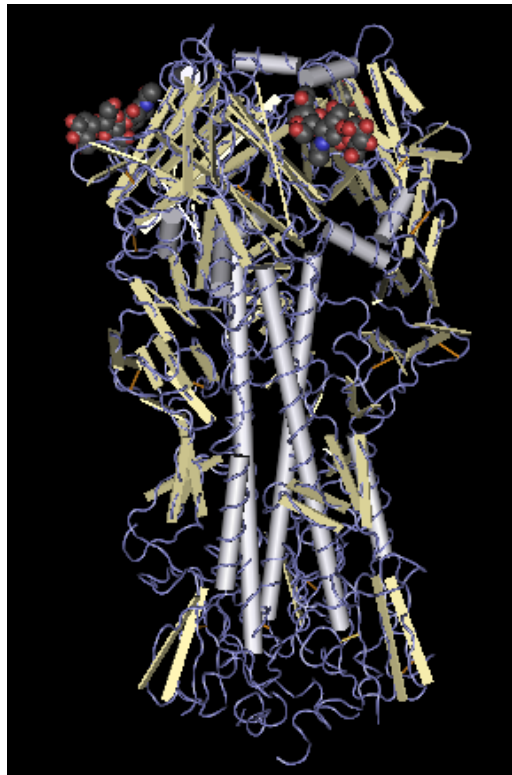
The avian influenza hemagglutinin binds alpha 2-3 sialic acid receptors, while human influenza hemagglutinins bind alpha 2-6 sialic acid receptors. This means when the H5N1 strain infects humans, it will replicate in the lower respiratory tract, and consequently will cause viral pneumonia. There is as yet no human form of H5N1, so all humans who have caught it so far have caught **avian** H5N1. In general, humans who catch a humanized influenza A virus (a human flu virus of type A) usually have symptoms that include fever, cough, sore throat, muscle aches, conjunctivitis, and, in severe cases, breathing problems and pneumonia that may be fatal. The severity of the infection depends in large part on the state of the infected person's immune system and whether the victim has been exposed to the strain before (in which case they would be partially immune). No one knows if these or other symptoms will be the symptoms of a humanized H5N1 flu.

The reported mortality rate of highly pathogenic H5N1 avian influenza in a human is high; WHO data indicate 60% of cases classified as H5N1 resulted in death. However, there is some evidence the actual mortality rate of avian flu could be much lower, as there

may be many people with milder symptoms who do not seek treatment and are not counted.

In one case, a boy with H5N1 experienced diarrhea followed rapidly by a coma without developing respiratory or flu-like symptoms. There have been studies of the levels of cytokines in humans infected by the H5N1 flu virus. Of particular concern is elevated levels of tumor necrosis factor-alpha, a protein associated with tissue destruction at sites of infection and increased production of other cytokines. Flu virus-induced increases in the level of cytokines is also associated with flu symptoms, including fever, chills, vomiting and headache. Tissue damage associated with pathogenic flu virus infection can ultimately result in death. The inflammatory cascade triggered by H5N1 has been called a 'cytokine storm' by some, because of what seems to be a positive feedback process of damage to the body resulting from immune system stimulation. H5N1 induces higher levels of cytokines than the more common flu virus types.

Genetics



The *H* in H5N1 stands for "Hemagglutinin", as depicted in this molecular model

The first known strain of HPAI A(H5N1) (called A/chicken/Scotland/59) killed two flocks of chickens in Scotland in 1959; but that strain was very different from the current highly pathogenic strain of H5N1. The dominant strain of HPAI A(H5N1) in 2004 evolved from 1999 to 2002 creating the Z genotype. It has also been called "Asian lineage HPAI A(H5N1)".

Asian lineage HPAI A(H5N1) is divided into two antigenic clades. "Clade 1 includes human and bird isolates from Vietnam, Thailand, and Cambodia and bird isolates from Laos and Malaysia. Clade 2 viruses were first identified in bird isolates from China, Indonesia, Japan, and South Korea before spreading westward to the Middle East, Europe, and Africa. The clade 2 viruses have been primarily responsible for human H5N1 infections that have occurred during late 2005 and 2006, according to WHO. Genetic analysis has identified six subclades of clade 2, three of which have a distinct geographic distribution and have been implicated in human infections: Map

- Subclade 1, Indonesia
- Subclade 2, Europe, Middle East, and Africa (called EMA)
- Subclade 3, China"

A 2007 study focused on the EMA subclade has shed further light on the EMA mutations. "The 36 new isolates reported here greatly expand the amount of whole-genome sequence data available from recent avian influenza (H5N1) isolates. Before our project, GenBank contained only 5 other complete genomes from Europe for the 2004–2006 period, and it contained no whole genomes from the Middle East or northern Africa. Our analysis showed several new findings. First, all European, Middle Eastern, and African samples fall into a clade that is distinct from other contemporary Asian clades, all of which share common ancestry with the original 1997 Hong Kong strain. Phylogenetic trees built on each of the 8 segments show a consistent picture of 3 lineages, as illustrated by the HA tree shown in Figure 1. Two of the clades contain exclusively Vietnamese isolates; the smaller of these, with 5 isolates, we label V1; the larger clade, with 9 isolates, is V2. The remaining 22 isolates all fall into a third, clearly distinct clade, labeled EMA, which comprises samples from Europe, the Middle East, and Africa. Trees for the other 7 segments display a similar topology, with clades V1, V2, and EMA clearly separated in each case. Analyses of all available complete influenza (H5N1) genomes and of 589 HA sequences placed the EMA clade as distinct from the major clades circulating in People's Republic of China, Indonesia, and Southeast Asia."

Terminology

H5N1 isolates are identified like this actual HPAI A(H5N1) example, **A/chicken/Nakorn-Patom/Thailand/CU-K2/04(H5N1)**:

- **A** stands for the species of influenza (A, B or C).
- **chicken** is the species the isolate was found in
- **Nakorn-Patom/Thailand** is the place this specific virus was isolated
- **CU-K2** identifies it from other influenza viruses isolated at the same place
- **04** represents the year 2004
- **H5** stands for the fifth of several known types of the protein hemagglutinin.
- **N1** stands for the first of several known types of the protein neuraminidase.

Other examples include: A/duck/Hong Kong/308/78(H5N3), A/avian/NY/01(H5N2), A/chicken/Mexico/31381-3/94(H5N2), and A/shoveler/Egypt/03(H5N2).

As with other avian flu viruses, H5N1 has strains called "highly pathogenic" (HP) and "low-pathogenic" (LP). Avian influenza viruses that cause HPAI are highly virulent, and mortality rates in infected flocks often approach 100%. LPAI viruses have negligible virulence, but these viruses can serve as progenitors to HPAI viruses. The current strain of H5N1 responsible for the deaths of birds across the world is an HPAI strain; all other current strains of H5N1, including a North American strain that causes no disease at all in any species, are LPAI strains. All HPAI strains identified to date have involved H5 and H7 subtypes. The distinction concerns pathogenicity in poultry, not humans. Normally a highly pathogenic avian virus is not highly pathogenic to either humans or non-poultry birds. This current deadly strain of H5N1 is unusual in being deadly to so many species, including some, like domestic cats, never previously susceptible to any influenza virus.

Genetic structure and related subtypes



The *N* in H5N1 stands for "Neuraminidase", the protein depicted in this ribbon diagram

H5N1 is a subtype of the species *Influenza A virus* of the *Influenzavirus A* genus of the *Orthomyxoviridae* family. Like all other influenza A subtypes, the H5N1 subtype is an RNA virus. It has a segmented genome of eight negative sense, single-strands of RNA, abbreviated as PB2, PB1, PA, HA, NP, NA, MP and NS.

HA codes for hemagglutinin, an antigenic glycoprotein found on the surface of the influenza viruses and is responsible for binding the virus to the cell that is being infected. NA codes for neuraminidase, an antigenic glycosylated enzyme found on the surface of the influenza viruses. It facilitates the release of progeny viruses from infected cells. The hemagglutinin (HA) and neuraminidase (NA) RNA strands specify the structure of proteins that are most medically relevant as targets for antiviral drugs and antibodies. HA and NA are also used as the basis for the naming of the different subtypes of influenza A viruses. This is where the *H* and *N* come from in *H5N1*.

Influenza A viruses are significant for their potential for disease and death in humans and other animals. Influenza A virus subtypes that have been confirmed in humans, in order of the number of known human pandemic deaths that they have caused, include:

- H1N1, which caused the 1918 flu pandemic ("Spanish flu") and currently is causing seasonal human flu and the 2009 flu pandemic ("swine flu")
- H2N2, which caused "Asian flu"
- H3N2, which caused "Hong Kong flu" and currently causes seasonal human flu
- H5N1, ("bird flu"), which is noted for having a strain (Asian-lineage HPAI H5N1) that kills over half the humans it infects, infecting and killing species that were never known to suffer from influenza viruses before (e.g. cats), being unable to be stopped by culling all involved poultry - some think due to being endemic in wild birds, and causing billions of dollars to be spent in flu pandemic preparation and preventiveness
- H7N7, which has unusual zoonotic potential and killed one person
- H1N2, which is currently endemic in humans and pigs and causes seasonal human flu
- H9N2, which has infected three people
- H7N2, which has infected two people
- H7N3, which has infected two people
- H10N7, which has infected two people

Low pathogenic H5N1

Low pathogenic avian influenza H5N1 (LPAI H5N1) also called "North American" H5N1 commonly occurs in wild birds. In most cases, it causes minor sickness or no noticeable signs of disease in birds. It is not known to affect humans at all. The only concern about it is that it is possible for it to be transmitted to poultry and in poultry mutate into a highly pathogenic strain.

- 1975 – LPAI H5N1 was detected in a wild mallard duck and a wild blue goose in Wisconsin.

- 1981 and 1985 – LPAI H5N1 was detected in ducks by the University of Minnesota conducting a sampling procedure in which sentinel ducks were monitored in cages placed in the wild for a short period of time.
- 1983 – LPAI H5N1 was detected in ring-billed gulls in Pennsylvania.
- 1986 - LPAI H5N1 was detected in a wild mallard duck in Ohio.
- 2005 - LPAI H5N1 was detected in ducks in Manitoba, Canada.
- 2008 - LPAI H5N1 was detected in ducks in New Zealand.
- 2009 - LPAI H5N1 was detected in commercial poultry in British Columbia.

"In the past, there was no requirement for reporting or tracking LPAI H5 or H7 detections in wild birds so states and universities tested wild bird samples independently of USDA. Because of this, the above list of previous detections might not be all inclusive of past LPAI H5N1 detections. However, the World Organization for Animal Health (OIE) recently changed its requirement of reporting detections of avian influenza. Effective in 2006, all confirmed LPAI H5 and H7 AI subtypes must be reported to the OIE because of their potential to mutate into highly pathogenic strains. Therefore, USDA now tracks these detections in wild birds, backyard flocks, commercial flocks and live bird markets."

High mutation rate

Influenza viruses have a relatively high mutation rate that is characteristic of RNA viruses. The segmentation of its genome facilitates genetic recombination by segment reassortment in hosts infected with two different influenza viruses at the same time. A previously uncontagious strain may then be able to pass between humans, one of several possible paths to a pandemic.

The ability of various influenza strains to show species-selectivity is largely due to variation in the hemagglutinin genes. Genetic mutations in the hemagglutinin gene that cause single amino acid substitutions can significantly alter the ability of viral hemagglutinin proteins to bind to receptors on the surface of host cells. Such mutations in avian H5N1 viruses can change virus strains from being inefficient at infecting human cells to being as efficient in causing human infections as more common human influenza virus types. This doesn't mean that one amino acid substitution can cause a pandemic, but it does mean that one amino acid substitution can cause an avian flu virus that is not pathogenic in humans to become pathogenic in humans.

Influenza A virus subtype H3N2 is endemic in pigs in China, and has been detected in pigs in Vietnam, increasing fears of the emergence of new variant strains. The dominant strain of annual flu virus in January 2006 was H3N2, which is now resistant to the standard antiviral drugs amantadine and rimantadine. The possibility of H5N1 and H3N2 exchanging genes through reassortment is a major concern. If a reassortment in H5N1 occurs, it might remain an H5N1 subtype, or it could shift subtypes, as H2N2 did when it evolved into the Hong Kong Flu strain of H3N2.

Both the H2N2 and H3N2 pandemic strains contained avian influenza virus RNA segments. "While the pandemic human influenza viruses of 1957 (H2N2) and 1968

(H3N2) clearly arose through reassortment between human and avian viruses, the influenza virus causing the 'Spanish flu' in 1918 appears to be entirely derived from an avian source".

Prevention

There are several H5N1 vaccines for several of the avian H5N1 varieties, but the continual mutation of H5N1 renders them of limited use to date: while vaccines can sometimes provide cross-protection against related flu strains, the best protection would be from a vaccine specifically produced for any future pandemic flu virus strain. Dr. Daniel Lucey, co-director of the Biohazardous Threats and Emerging Diseases graduate program at Georgetown University has made this point, "There is no H5N1 pandemic so there can be no pandemic vaccine". However, "pre-pandemic vaccines" have been created; are being refined and tested; and do have some promise both in furthering research and preparedness for the next pandemic. Vaccine manufacturing companies are being encouraged to increase capacity so that if a pandemic vaccine is needed, facilities will be available for rapid production of large amounts of a vaccine specific to a new pandemic strain.

Public health

"The United States is collaborating closely with eight international organizations, including the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and 88 foreign governments to address the situation through planning, greater monitoring, and full transparency in reporting and investigating avian influenza occurrences. The United States and these international partners have led global efforts to encourage countries to heighten surveillance for outbreaks in poultry and significant numbers of deaths in migratory birds and to rapidly introduce containment measures. The U.S. Agency for International Development (USAID) and the U.S. Department of State, the U.S. Department of Health and Human Services (HHS), and Agriculture (USDA) are coordinating future international response measures on behalf of the White House with departments and agencies across the federal government".

Together steps are being taken to "minimize the risk of further spread in animal populations", "reduce the risk of human infections", and "further support pandemic planning and preparedness".

Ongoing detailed mutually coordinated onsite surveillance and analysis of human and animal H5N1 avian flu outbreaks are being conducted and reported by the USGS National Wildlife Health Center, the Centers for Disease Control and Prevention, the World Health Organization, the European Commission, and others.

Treatment

There is no highly effective treatment for H5N1 flu, but oseltamivir (commercially marketed by Roche as Tamiflu), can sometimes inhibit the influenza virus from spreading inside the user's body. This drug has become a focus for some governments and organizations trying to prepare for a possible H5N1 pandemic. On April 20, 2006, Roche AG announced that a stockpile of three million treatment courses of Tamiflu are waiting at the disposal of the World Health Organization to be used in case of a flu pandemic; separately Roche donated two million courses to the WHO for use in developing nations that may be affected by such a pandemic but lack the ability to purchase large quantities of the drug.

However, WHO expert Hassan al-Bushra has said:

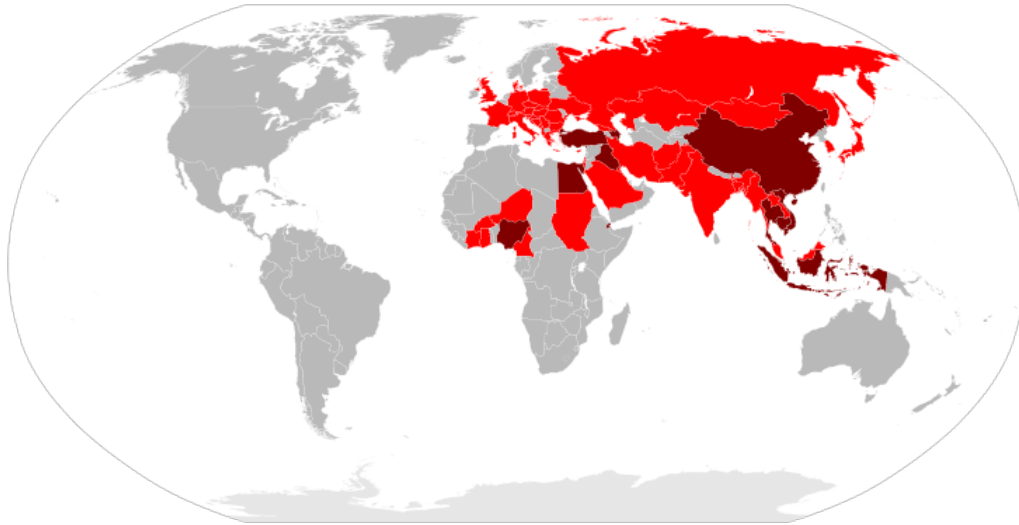
"Even now, we remain unsure about Tamiflu's real effectiveness. As for a vaccine, work cannot start on it until the emergence of a new virus, and we predict it would take six to nine months to develop it. For the moment, we cannot by any means count on a potential vaccine to prevent the spread of a contagious influenza virus, whose various precedents in the past 90 years have been highly pathogenic".

Animal and lab studies suggest that Relenza (zanamivir), which is in the same class of drugs as Tamiflu, may also be effective against H5N1. In a study performed on mice in 2000, "zanamivir was shown to be efficacious in treating avian influenza viruses H9N2, H6N1, and H5N1 transmissible to mammals". In addition, mice studies suggest the combination of zanamivir, celecoxib and mesalazine looks promising producing a 50% survival rate compared to no survival in the placebo arm. While no one knows if zanamivir will be useful or not on a yet to exist pandemic strain of H5N1, it might be useful to stockpile zanamivir as well as oseltamivir in the event of an H5N1 influenza pandemic. Neither oseltamivir nor zanamivir can currently be manufactured in quantities that would be meaningful once efficient human transmission starts. In September, 2006, a WHO scientist announced that studies had confirmed cases of H5N1 strains resistant to Tamiflu and Amantadine. Tamiflu-resistant strains have also appeared in the EU, which remain sensitive to Relenza.

Epidemiology

The earliest infections of humans by H5N1 coincided with an epizootic (an epidemic in nonhumans) of H5N1 influenza in Hong Kong's poultry population. This panzootic (a disease affecting animals of many species, especially over a wide area) outbreak was stopped by the killing of the entire domestic poultry population within the territory. However, the disease has continued to spread. On December 21, 2009 the WHO announced a total of 447 cases which resulted in the deaths of 263.

Contagiousness



Highly pathogenic H5N1

- Countries with poultry or wild birds killed by H5N1.
- Countries with humans, poultry and wild birds killed by H5N1.

H5N1 is easily transmissible between birds facilitating a potential global spread of H5N1. While H5N1 undergoes mutation and reassortment, creating variations which can infect species not previously known to carry the virus, not all of these variant forms can infect humans. H5N1 as an avian virus preferentially binds to a type of galactose receptors that populate the avian respiratory tract from the nose to the lungs and are virtually absent in humans, occurring only in and around the alveoli, structures deep in the lungs where oxygen is passed to the blood. Therefore, the virus is not easily expelled by coughing and sneezing, the usual route of transmission.

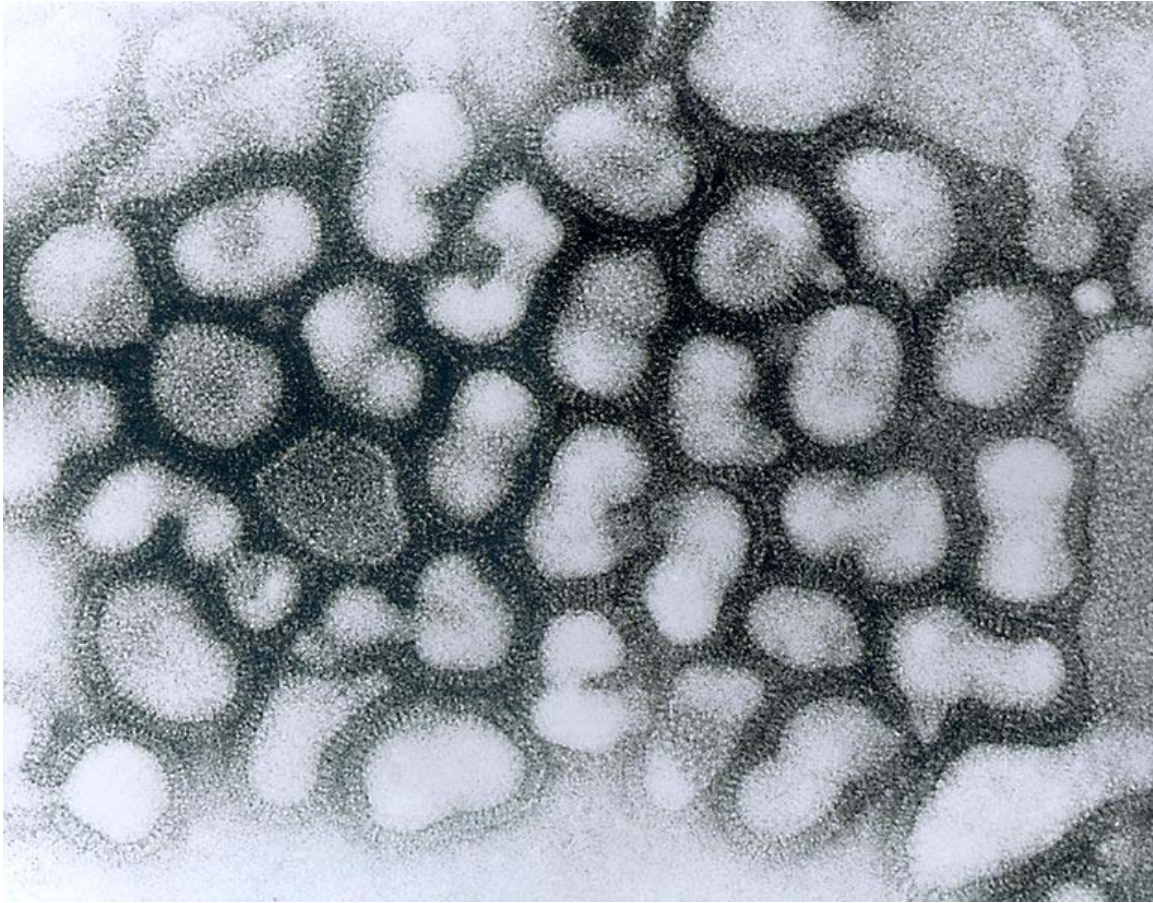
H5N1 is mainly spread by domestic poultry, both through the movements of infected birds and poultry products and through the use of infected poultry manure as fertilizer or feed. Humans with H5N1 have typically caught it from chickens, which were in turn infected by other poultry or waterfowl. Migrating waterfowl (wild ducks, geese and swans) carry H5N1, often without becoming sick. Many species of birds and mammals can be infected with HPAI A(H5N1), but the role of animals other than poultry and waterfowl as disease-spreading hosts is unknown.

According to a report by the World Health Organization, H5N1 may be spread indirectly. The report stated that the virus may sometimes stick to surfaces or get kicked up in fertilizer dust to infect people.

Virulence

H5N1 has mutated into a variety of strains with differing pathogenic profiles, some pathogenic to one species but not others, some pathogenic to multiple species. Each specific known genetic variation is traceable to a virus isolate of a specific case of infection. Through antigenic drift, H5N1 has mutated into dozens of highly pathogenic varieties divided into genetic clades which are known from specific isolates, but all currently belonging to genotype Z of avian influenza virus H5N1, now the dominant genotype. H5N1 isolates found in Hong Kong in 1997 and 2001 were not consistently transmitted efficiently among birds and did not cause significant disease in these animals. In 2002 new isolates of H5N1 were appearing within the bird population of Hong Kong. These new isolates caused acute disease, including severe neurological dysfunction and death in ducks. This was the first reported case of lethal influenza virus infection in wild aquatic birds since 1961. Genotype Z emerged in 2002 through reassortment from earlier highly pathogenic genotypes of H5N1 that first infected birds in China in 1996, and first infected humans in Hong Kong in 1997. Genotype Z is endemic in birds in Southeast Asia, has created at least two clades that can infect humans, and is spreading across the globe in bird populations. Mutations are occurring within this genotype that are increasing their pathogenicity. Birds are also able to shed the virus for longer periods of time before their death, increasing the transmissibility of the virus.

Transmission and host range



Influenza A virus, the virus that causes Avian flu. Transmission electron micrograph of negatively stained virus particles in late passage.

Infected birds transmit H5N1 through their saliva, nasal secretions, feces and blood. Other animals may become infected with the virus through direct contact with these bodily fluids or through contact with surfaces contaminated with them. H5N1 remains infectious after over 30 days at 0 °C (32.0 °F) (over one month at freezing temperature) or 6 days at 37 °C (98.6 °F) (one week at human body temperature) so at ordinary temperatures it lasts in the environment for weeks. In Arctic temperatures, it doesn't degrade at all.

Because migratory birds are among the carriers of the highly pathogenic H5N1 virus, it is spreading to all parts of the world. H5N1 is different from all previously known highly pathogenic avian flu viruses in its ability to be spread by animals other than poultry.

In October 2004, researchers discovered that H5N1 is far more dangerous than was previously believed. Waterfowl were revealed to be directly spreading the highly pathogenic strain of H5N1 to chickens, crows, pigeons, and other birds, and the virus was increasing its ability to infect mammals as well. From this point on, avian flu experts

increasingly referred to containment as a strategy that can delay, but not ultimately prevent, a future avian flu pandemic.

"Since 1997, studies of influenza A (H5N1) indicate that these viruses continue to evolve, with changes in antigenicity and internal gene constellations; an expanded host range in avian species and the ability to infect felids; enhanced pathogenicity in experimentally infected mice and ferrets, in which they cause systemic infections; and increased environmental stability."

The New York Times, in an article on transmission of H5N1 through smuggled birds, reports Wade Hagemeyer of Wetlands International stating, "We believe it is spread by both bird migration and trade, but that trade, particularly illegal trade, is more important".

On September 27, 2007 researchers reported that the H5N1 bird flu virus can also pass through a pregnant woman's placenta to infect the fetus. They also found evidence of what doctors had long suspected—that the virus not only affects the lungs, but also passes throughout the body into the gastrointestinal tract, the brain, liver, and blood cells.

Society and culture

H5N1 has had a huge effect on human society, especially the financial, political, social, and personal responses to both actual and predicted deaths in birds, humans, and other animals. Billions of U.S. dollars are being raised and spent to research H5N1 and prepare for a potential avian influenza pandemic. Over ten billion dollars have been spent and over two hundred million birds killed to try to contain H5N1.

People have reacted by buying less chicken causing poultry sales and prices to fall. Many individuals have stockpiled supplies for a possible flu pandemic. International health officials and other experts have pointed out that many unknown questions still hover around the disease.

Dr. David Nabarro, Chief Avian Flu Coordinator for the United Nations, and former Chief of Crisis Response for the World Health Organization has described himself as "quite scared" about H5N1's potential impact on humans. Nabarro has been accused of being alarmist before and on his first day in his role for the United Nations he proclaimed the avian flu could kill 150 million people. In an interview with the International Herald Tribune, Nabarro compares avian flu to AIDS in Africa, warning that underestimations led to inappropriate focus for research and intervention.

Chapter 10

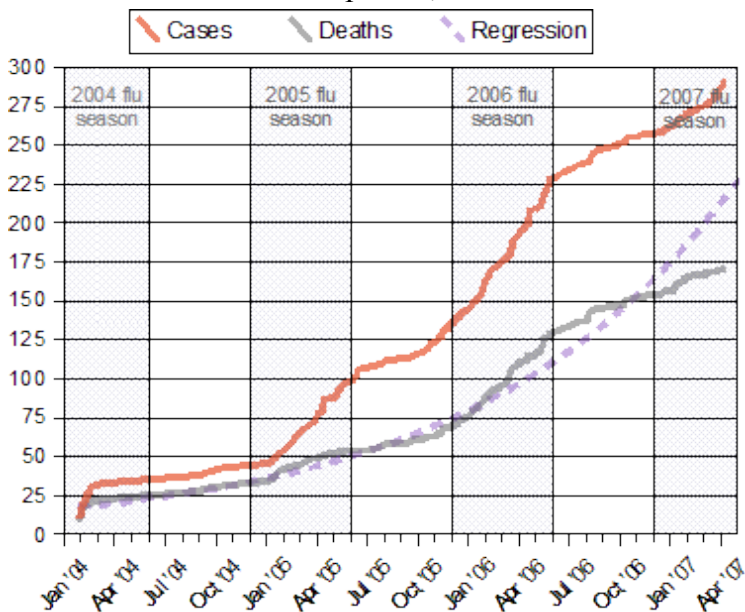
Transmission and Infection of H5N1

Transmission and infection of H5N1 from infected avian sources to humans is a concern due to the global spread of H5N1 that constitutes a pandemic threat.

Infected birds pass on H5N1 through their saliva, nasal secretions, and feces. Other birds may pick up the virus through direct contact with these excretions or when they have contact with surfaces contaminated with this material. Because migratory birds are among the carriers of the H5N1 virus it may spread to all parts of the world. Past outbreaks of avian flu have often originated in crowded conditions in southeast and east Asia, where humans, pigs, and poultry live in close quarters. In these conditions a virus is more likely to mutate into a form that more easily infects humans. A few isolated cases of suspected human to human transmission exist, with the latest such case in June 2006 (among members of a family in Sumatra). No pandemic strain of H5N1 has yet been found.

Cumulative Human Cases of and Deaths from H5N1

As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007." Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

H5N1 vaccines for chickens exist and are sometimes used, although there are many difficulties, and it's difficult to decide whether it helps more or hurts more. H5N1 pre-pandemic vaccines exist in quantities sufficient to inoculate a few million people and might be useful for priming to "boost the immune response to a different H5N1 vaccine tailor-made years later to thwart an emerging pandemic". H5N1 pandemic vaccines and technologies to rapidly create them are in the H5N1 clinical trials stage but can not be verified as useful until after there exists a pandemic strain.

Environmental survival

Avian flu virus can last indefinitely at a temperature dozens of degrees below freezing, as is found in the northern most areas that migratory birds frequent.

Heat kills H5N1 (i.e. inactivates the virus).

Influenza A viruses can survive:

- Over 30 days at 0°C (32.0°F) (over one month at freezing temperature)
- 6 days at 37°C (98.6°F) (one week at human body temperature)
- decades in permanently frozen lakes
- on hard non-porous surface such as plastic or stainless steel for 24–48 hours
- on clothes, paper and tissues for 8–12 hours

While cooking poultry to 70°C (158°F) kills the H5N1 virus, it is recommended to cook meat to 74°C (165°F) to kill all foodborne pathogens.

Inactivation of the virus also occurs under the following conditions:

- 30 minutes 60°C (140.0°F) (half hour at a temperature that causes first and second degree burns in humans in ten seconds)
- Acidic pH conditions
- Presence of oxidizing agents such as sodium dodecyl sulfate, lipid solvents, and B-propiolactone
- Exposure to disinfectants: formalin, iodine compounds

Ordinary levels of chlorine in tap water kill H5N1 in public water systems.

To kill avian flu viruses, the "World Health Organization recommends that environmental surfaces be cleaned by the following:

- Disinfectants such as sodium hypochloride, 1% in-use dilution, 5% solution to be diluted 1:5 in clean water, for materials contaminated with blood and body fluids
- Bleaching powder seven grams per liter with 70% available chlorine for toilets and bathrooms
- 70% alcohol for smooth surfaces, tabletops, and other surfaces where bleach cannot be used"

H5N1 "can remain infectious in municipal landfills for almost 2 years. [...] The two factors that most reduced influenza survival times were elevated temperature and acidic or alkaline pH."

Avian flu in birds

According to *Avian Influenza* by Timm C. Harder and Ortrud Werner:

Following an incubation period of usually a few days (but rarely up to 21 days), depending upon the characteristics of the isolate, the dose of inoculum, the species, and age of the bird, the clinical presentation of avian influenza in birds is variable and symptoms are fairly unspecific. Therefore, a diagnosis solely based on the clinical presentation is impossible. The symptoms following infection with low pathogenic AIV may be as discrete as ruffled feathers, transient reductions in egg production or weight loss combined with a slight respiratory disease. Some LP strains such as certain Asian H9N2 lineages, adapted to efficient replication in poultry, may cause more prominent signs and also significant mortality. In its highly pathogenic form, the illness in chickens and turkeys is characterised by a sudden onset of severe symptoms and a mortality that can approach 100% within 48 hours.

The current method of prevention in animal populations is to destroy infected animals, as well as animals suspected of being infected. In southeast Asia, millions of domestic birds have been slaughtered to prevent the spread of the virus.

Poultry farming practices

There have been a number of farming practices that have changed in response to outbreaks of the H5N1 virus, including:

- vaccinating poultry against bird flu
- vaccinating poultry workers against human flu
- limiting travel in areas where H5N1 is found
- increasing farm hygiene
- reducing contact between livestock and wild birds
- reducing open-air wet markets

- limiting workers contact with cock fighting
- reducing purchases of live fowl
- improving veterinary vaccine availability and cost.

For example, after nearly two years of using mainly culling to control the virus, the Vietnamese government in 2005 adopted a combination of mass poultry vaccination, disinfecting, culling, information campaigns and bans on live poultry in cities.

Dealing with outbreaks

The majority of H5N1 flu cases have been reported in southeast and east Asia. Once an outbreak is detected, local authorities often order a mass slaughter of birds or animals affected. If this is done promptly, an outbreak of avian flu may be prevented. However, the United Nations (UN) World Health Organization (WHO) has expressed concern that not all countries are reporting outbreaks as completely as they should. China, for example, is known to have initially denied past outbreaks of severe acute respiratory syndrome (SARS) and HIV, although there have been some signs of improvement regarding its openness, particularly with regard to H5N1.

Use of vaccines

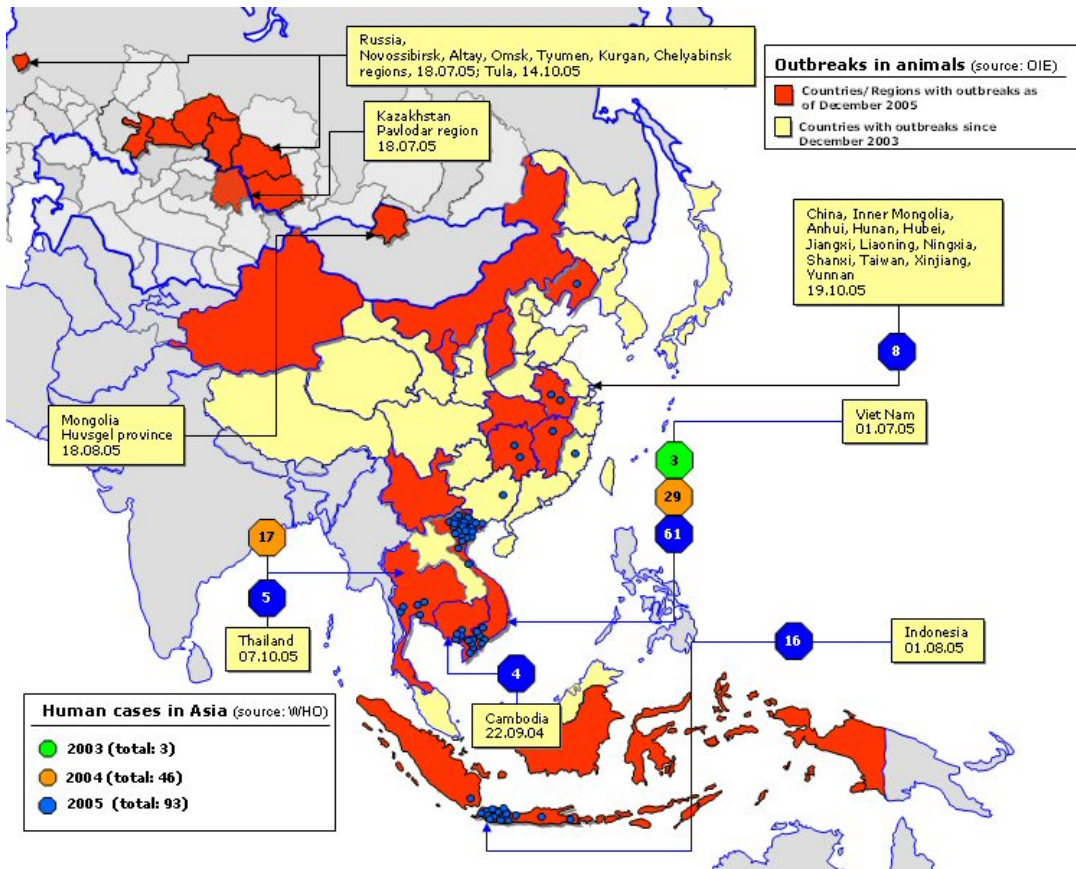
Dr. Robert G. Webster *et al.* write

Transmission of highly pathogenic H5N1 from domestic poultry back to migratory waterfowl in western China has increased the geographic spread. The spread of H5N1 and its likely reintroduction to domestic poultry increase the need for good agricultural vaccines. In fact, the root cause of the continuing H5N1 pandemic threat may be the way the pathogenicity of H5N1 viruses is masked by cocirculating influenza viruses or bad agricultural vaccines."

Webster speculates that substandard vaccines may be preventing the expression of the disease in the birds but not stopping them from carrying or transmitting the virus through feces, or the virus from mutating.

In order to protect their poultry from death from H5N1, China reportedly made a vaccine based on reverse genetics produced with H5N1 antigens, that Dr Wendy Barclay, a virologist at the University of Reading believes have generated up to six variations of H5N1.

Transmission



The spread of avian influenza in the eastern hemisphere

According to the United Nations FAO, wild water fowl likely plays a role in the avian influenza cycle and could be the initial source for AI viruses, which may be passed on through contact with resident water fowl or domestic poultry, particularly domestic ducks. A newly mutated virus could circulate within the domestic and possibly resident bird populations until highly pathogenic avian influenza (HPAI) arises. This new virus is pathogenic to poultry and possibly to the wild birds that it arose from.

Wild birds found to have been infected with HPAI were either sick or dead. This could possibly affect the ability of these birds to carry HPAI for long distances. However, the findings in Qinghai Lake-China, suggest that H5N1 viruses could possibly be transmitted between migratory birds. Additionally, the new outbreaks of HPAI in poultry and wild birds in Russia, Kazakhstan, Western China and Mongolia may indicate that migratory birds probably act as carriers for the transport of HPAI over longer distances. Short distance transmission between farms, villages or contaminated local water bodies is likewise a distinct possibility.

The AI virus has adapted to the environment in ways such as using water for survival and to spread, and creating a reservoir (ducks) strictly tied to water. The water in turn

influences movement, social behavior and migration patterns of water bird species. It is therefore of great importance to know the ecological strategy of influenza virus as well, in order to fully understand this disease and to control outbreaks when they occur. Most research is needed concerning HPAI viruses in wild birds. For example, small birds like sparrows, starlings and pigeons can be infected with deadly H5N1 strains and they can carry the virus from chicken house to chicken house causing massive epidemics among the chickens.

Avian flu in humans

Human to human transmission

The WHO believes that another influenza pandemic is as likely to occur at any time since 1968, when the last century's third of three pandemics took place. The WHO describes a series of six phases, starting with the inter-pandemic period, where there are no new influenza virus subtypes detected in humans, and progressing numerically to the pandemic period, where there is efficient and sustained human-to-human transmission of the virus in the general population. At the present moment, we are at phase 3 on the scale, meaning a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and sustainably among humans.

So far, H5N1 infections in humans are attributed to bird-to-human transmission of the virus in most cases. Until May 2006, the WHO estimate of the number of human to human transmission had been "two or three cases". On May 24, 2006, Dr. Julie L. Gerberding, director of the United States Centers for Disease Control and Prevention in Atlanta, estimated that there had been "at least three." On May 30, Maria Cheng, a WHO spokeswoman, said there were "probably about half a dozen," but that no one "has got a solid number." A few isolated cases of suspected human to human transmission exist, with the latest such case in June 2006 (among members of a family in Sumatra). No pandemic strain of H5N1 has yet been found.

There is also concern, although no definitive proof, that other animals — particularly cats — may be able to act as a bridge between birds and humans. So far several cats have been confirmed to have died from H5N1 and the fact that cats have regular close contact with both birds and humans means monitoring of H5N1 in cats, and dogs will need to continue.

Prevention

Notwithstanding possible mutation of the virus, the probability of a "humanized" form of H5N1 emerging through genetic recombination in the body of a human co-infected with H5N1 and another influenza virus type (a process called reassortment) could be reduced by widespread seasonal influenza vaccination in the general population. It is not clear at this point whether vaccine production and immunization could be stepped up sufficiently to meet this demand.

If an outbreak of pandemic flu does occur, its spread might be slowed by increasing hygiene in aircraft, and by examining airline cabin air filters for presence of H5N1 virus.

The American Centers for Disease Control and Prevention advises travelers to areas of Asia where outbreaks of H5N1 have occurred to avoid poultry farms and animals in live food markets . Travelers should also avoid surfaces that appear to be contaminated by feces from any kind of animal, especially poultry.

There are several H5N1 vaccines for several of the avian H5N1 varieties. H5N1 continually mutates rendering them, so far for humans, of little use. While there can be some cross-protection against related flu strains, the best protection would be from a vaccine specifically produced for any future pandemic flu virus strain. Dr. Daniel Lucey, co-director of the Biohazardous Threats and Emerging Diseases graduate program at Georgetown University has made this point, "There is no H5N1 pandemic so there can be no pandemic vaccine." However, "pre-pandemic vaccines" have been created; are being refined and tested; and do have some promise both in furthering research and preparedness for the next pandemic . Vaccine manufacturing companies are being encouraged to increase capacity so that if a pandemic vaccine is needed, facilities will be available for rapid production of large amounts of a vaccine specific to a new pandemic strain.

It is not likely that use of antiviral drugs could prevent the evolution of a pandemic flu virus.

Symptoms

The human incubation period of avian influenza A (H5N1) is 2 to 17 days. Once infected, the virus can spread by cell-to-cell contact, bypassing receptors. So even if a strain is very hard to initially catch, once infected, it spreads rapidly within a body. For highly pathogenic H5N1 avian influenza in a human, "the time from the onset to presentation (median, 4 days) or to death (median, 9 to 10 days) has remained unchanged from 2003 through 2006."

Avian influenza HA bind alpha 2-3 sialic acid receptors while human influenza HA bind alpha 2-6 sialic acid receptors. Usually other differences also exist. There is as yet no human form of H5N1, so all humans who have caught it so far have caught **avian** H5N1.

Human flu symptoms usually include fever, cough, sore throat, muscle aches, conjunctivitis and, in severe cases, severe breathing problems and pneumonia that may be fatal. The severity of the infection will depend to a large part on the state of the infected person's immune system and if the victim has been exposed to the strain before, and is therefore partially immune. No one knows if these or other symptoms will be the symptoms of a humanized H5N1 flu.

Highly pathogenic H5N1 avian influenza in a human appears to be far worse, killing over 50% of humans reported infected with the virus, although it is unknown how many cases

(with milder symptoms) go unreported. In one case, a boy with H5N1 experienced diarrhea followed rapidly by a coma without developing respiratory or flu-like symptoms.

As of February 2008, the "median age of patients with influenza A (H5N1) virus infection is approximately 18 years [...] The overall case fatality proportion is 61% [...] Handling of sick or dead poultry during the week before the onset of illness is the most commonly recognized risk factor [...] The primary pathologic process that causes death is fulminant viral pneumonia."

There have been studies of the levels of cytokines in humans infected by the H5N1 flu virus. Of particular concern is elevated levels of tumor necrosis factor-alpha (TNF α), a protein that is associated with tissue destruction at sites of infection and increased production of other cytokines. Flu virus-induced increases in the level of cytokines is also associated with flu symptoms including fever, chills, vomiting and headache. Tissue damage associated with pathogenic flu virus infection can ultimately result in death. The inflammatory cascade triggered by H5N1 has been called a 'cytokine storm' by some, because of what seems to be a positive feedback process of damage to the body resulting from immune system stimulation. H5N1 type flu virus induces higher levels of cytokines than the more common flu virus types such as H1N1. Other important mechanisms also exist "in the acquisition of virulence in avian influenza viruses" according to the CDC.

The NS1 protein of the highly pathogenic avian H5N1 viruses circulating in poultry and waterfowl in Southeast Asia is currently believed to be responsible for the enhanced proinflammatory cytokine response. H5N1 NS1 is characterized by a single amino acid change at position 92. By changing the amino acid from glutamic acid to aspartic acid, researchers were able to abrogate the effect of the H5N1 NS1. This single amino acid change in the NS1 gene greatly increased the pathogenicity of the H5N1 influenza virus.

In short, this one amino acid difference in the NS1 protein produced by the NS RNA molecule of the H5N1 virus is believed to be largely responsible for an increased pathogenicity (on top of the already increased pathogenicity of its hemagglutinin type which allows it to grow in organs other than lungs) that can manifest itself by causing a cytokine storm in a patient's body, often causing pneumonia and death.

Treatment

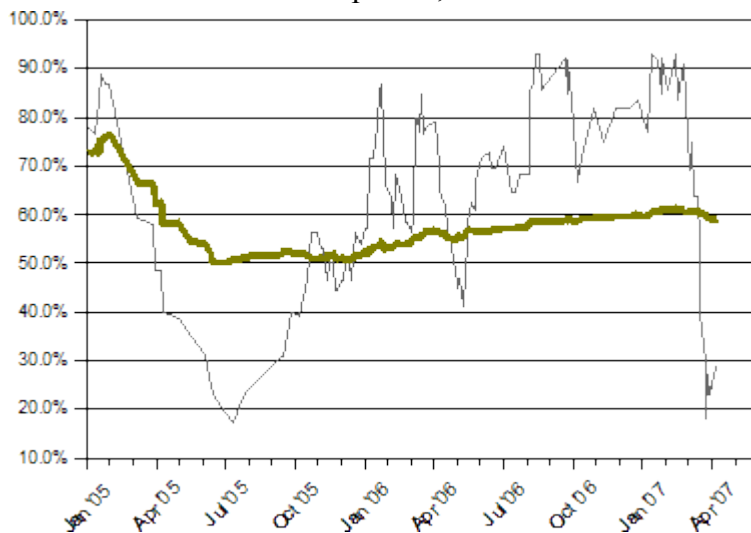
Neuraminidase inhibitors are a class of drugs that includes zanamivir and oseltamivir, the latter being licensed for prophylaxis treatment in the United Kingdom. Oseltamivir inhibits the influenza virus from spreading inside the user's body. It is marketed by Roche as *Tamiflu*. This drug has become a focus for some governments and organizations trying to be seen as making preparations for a possible H5N1 pandemic. In August 2005, Roche agreed to donate three million courses of Tamiflu to be deployed by the WHO to contain a pandemic in its region of origin. Although *Tamiflu* is patented, international law gives governments wide freedom to issue compulsory licenses for life-saving drugs.

A second class of drugs, which include amantadine and rimantadine, target the M2 protein, but have become ineffective against most strains of H5N1, due to their use in poultry in China in the 1990s, which created resistant strains.. However, recent data suggest that some strains of H5N1 are susceptible to the older drugs, which are inexpensive and widely available.

Research indicates that therapy to block one cytokine to lessen a cytokine storm in a patient may not be clinically beneficial.

Mortality rate

Human Mortality from H5N1
As of April 11, 2007



- The thin line represents average mortality of recent cases. The thicker line represents mortality averaged over all cases.
- According to WHO: "*Assessment of mortality rates and the time intervals between symptom onset and hospitalization and between symptom onset and death suggests that the illness pattern has not changed substantially during the three years.*"

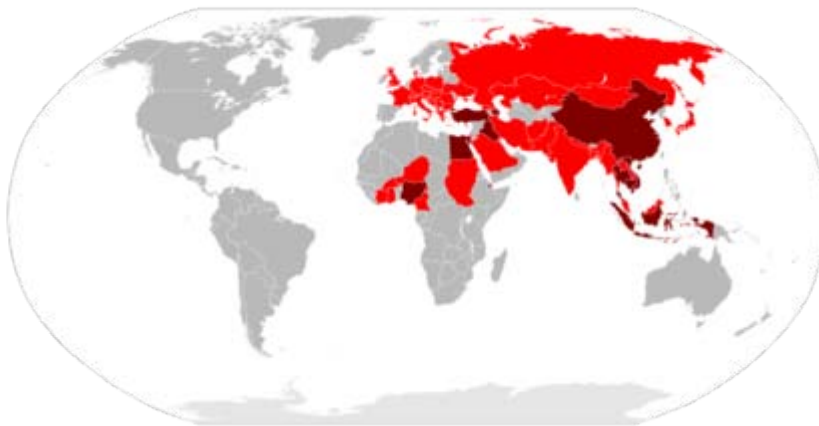
From the first laboratory-confirmed case through March 18, 2008, the number confirmed human cases of H5N1 reported to WHO stands at 373, with 236 fatalities, reflecting a 63.27% fatality rate.

The global case fatality ratio looks only to the official tally of cases confirmed by the WHO. It takes no account of other cases, such as those appearing in press reports. Nor does it reflect any estimate of the global extent of mild, asymptomatic, or other cases which are undiagnosed, unreported by national governments to the WHO, or for any reason cannot be confirmed by the WHO. While the WHO's case count is clearly the most authoritative, these unavoidable limitations result in an unknown number of cases being omitted from it.

Chapter 11

Global Spread of H5N1

Highly pathogenic H5N1



Countries that have reported deaths of poultry or wild birds linked to highly pathogenic H5N1 infection.

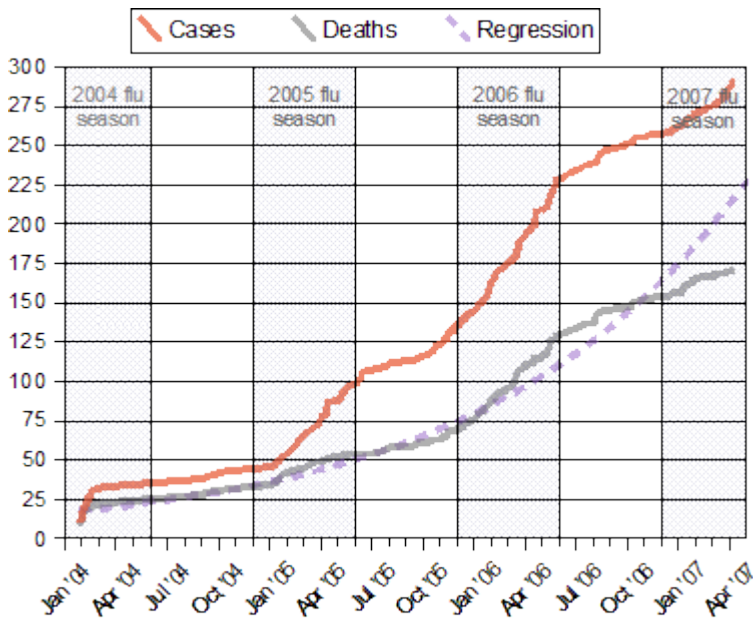
Countries that have reported human cases of highly pathogenic H5N1 infection.

The **global spread of highly pathogenic H5N1 influenza** in birds is considered a significant pandemic threat.

While other H5N1 influenza strains are known, they are significantly different from a current, highly pathogenic H5N1 strain on a genetic level, making the global spread of this new strain unprecedented. The H5N1 strain is a fast-mutating, highly pathogenic avian influenza virus (HPAI) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species especially over a wide area).

"Since 1997, studies of H5N1 influenza indicate that these viruses continue to evolve, with changes in antigenicity and internal gene constellations; an expanded host range in avian species and the ability to infect felids; enhanced pathogenicity in experimentally infected mice and ferrets, in which they cause systemic infections; and increased environmental stability."

Cumulative Human Cases of and Deaths from H5N1 As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007." Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

Tens of millions of birds have died of H5N1 influenza and hundreds of millions of birds have been slaughtered and disposed of, to limit the spread of H5N1. Countries that have reported one or more major highly pathogenic H5N1 outbreaks in birds (causing at least thousands but in some cases millions of dead birds) are (in order of first outbreak occurrence): Korea, Vietnam, Japan, Thailand, Cambodia, Laos, Indonesia, China, Malaysia, Russia, Kazakhstan, Mongolia, Turkey, Romania, Croatia, Ukraine, Cyprus, Iraq, Nigeria, Egypt, India, France, Niger, Bosnia, Azerbaijan, Albania, Cameroon, Myanmar, Afghanistan, Israel, Pakistan, Jordan, Burkina Faso, Germany, Sudan, Ivory Coast, Djibouti, Hungary, United Kingdom, Kuwait, Bangladesh, Saudi Arabia, Ghana, Czech Republic, Togo, Nepal.

Highly pathogenic H5N1 has been found in birds in the wild in numerous other countries: Austria, Bulgaria, Denmark, Greece, Iran, Italy, Poland, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland. Surveillance of H5N1 in humans, poultry, wild birds, cats and other animals remains very weak in many parts of Asia and Africa. Much remains unknown about the exact extent of its spread.

H5N1 has low pathogenic varieties endemic in birds in North America. H5N1 has a highly pathogenic variety that is endemic in dozens of species of birds throughout south Asia and parts of Africa. So far, it is very difficult for humans to become infected with H5N1. The presence of highly pathogenic (deadly) H5N1 around the world in both birds in the wild (swans, magpies, ducks, geese, pigeons, eagles, etc.) and in chickens and turkeys on farms has been demonstrated in millions of cases with the virus isolate actually sequenced in hundreds of cases yielding definitive proof of the evolution of this strain of this subtype of the species Influenzavirus A (bird flu virus).

According to Robert G. Webster:

"The epicenters of both the Asian influenza pandemic of 1957 and the Hong Kong influenza pandemic of 1968 were in Southeast Asia, and it is in this region that multiple clades of H5N1 influenza virus have already emerged. The Asian H5N1 virus was first detected in Guangdong Province, China, in 1996, when it killed some geese, but it received little attention until it spread through live-poultry markets in Hong Kong to humans in May 1997, killing 6 of 18 infected people. [...] From 1997 to May 2005, H5N1 viruses were largely confined to Southeast Asia, but after they had infected wild birds in Qinghai Lake, China, they rapidly spread westward. [...] The intermittent spread to humans will continue, and the virus will continue to evolve."Map

As of the July 25, 2008 FAO Avian Influenza Disease Emergency Situation Update, H5N1 pathogenicity is continuing to gradually rise in endemic areas but the avian influenza disease situation in farmed birds is being held in check by vaccination. Eleven outbreaks of H5N1 were reported worldwide in June 2008 in five countries (China, Egypt, Indonesia, Pakistan and Viet Nam) compared to 65 outbreaks in June 2006 and 55 in June 2007. The "global HPAI situation can be said to have improved markedly in the first half of 2008 [but] cases of HPAI are still underestimated and underreported in many countries because of limitations in country disease surveillance systems".

Human and bird cases

1959–1997



Ducks play a key role in H5N1 spread

- A highly pathogenic strain of H5N1 caused flu outbreaks with significant spread to numerous farms, resulting in great economic losses in 1959 in Scotland in chickens and in 1991 in England in turkeys. These strains were somewhat similar to the current pathogenic strain of H5N1 in two of its ten genes, the gene that causes it to be type H5 and the gene that causes it to be N1. The other genes can and have been reassorted from other subtypes of the bird flu species (their ease at exchanging genes is part of what makes them all one species). Evolution by reassortment of H5N1 from 1999 to 2002 created the Z genotype which became the dominant strain of highly pathogenic H5N1 in 2004 and is now spreading across the entire world in both wild and domestic birds.
- "The precursor of the H5N1 influenza virus that spread to humans in 1997 was first detected in Guangdong, China, in 1996, when it caused a moderate number of deaths in geese and attracted very little attention."
- In 1997, in Hong Kong, 18 humans were infected and 6 died in the first known case of H5N1 infecting humans.
- On 28 December to 29 December 1997, 1.3 million chickens were killed by Hong Kong Government. The government also suspended the import of chickens from mainland China.

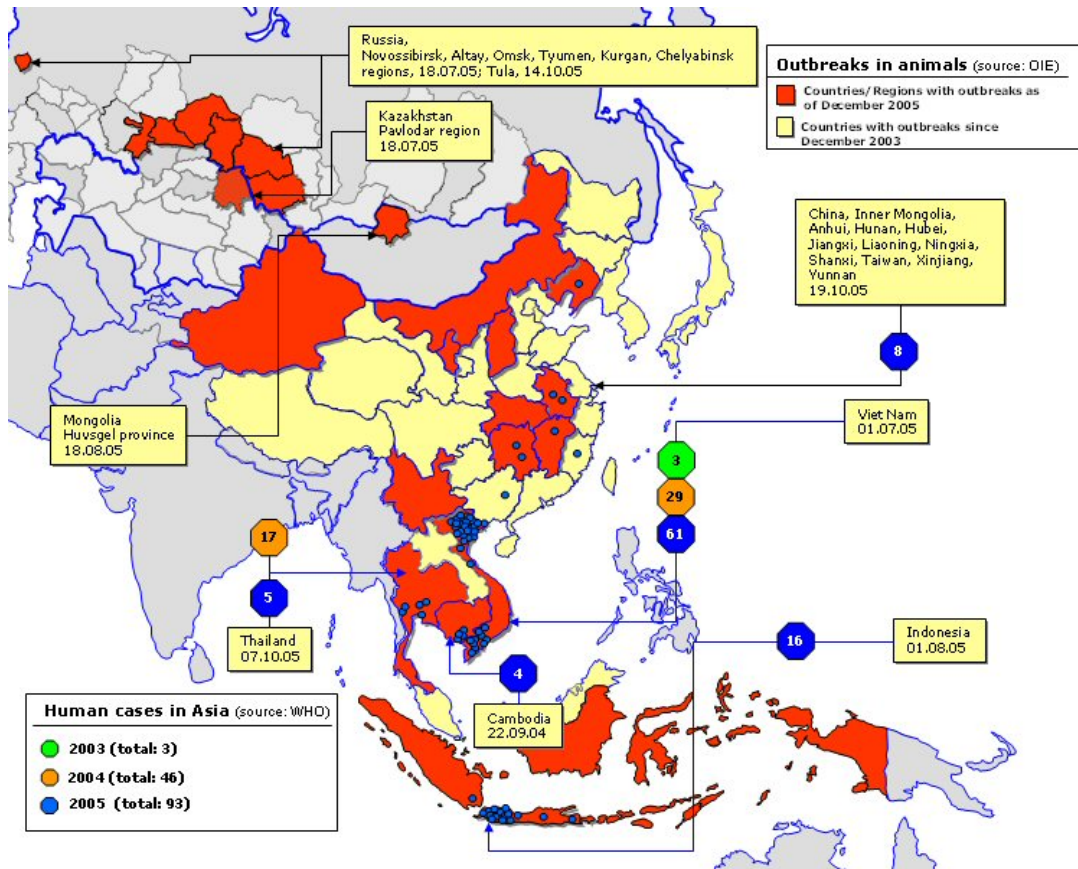
2003

- "Human disease associated with influenza A subtype H5N1 re-emerged in January 2003, for the first time since an outbreak in Hong Kong in 1997." Three people in one family were infected after visiting Fujian province in mainland China and 2 died.
- By midyear of 2003 outbreaks of poultry disease caused by H5N1 occurred in Asia, but were not recognized as such. That December animals in a Thai zoo died after eating infected chicken carcasses. Later that month H5N1 infection was detected in 3 flocks in the Republic of Korea.
- H5N1 in China in this and later periods is less than fully reported. Blogs have described many discrepancies between official China government announcements concerning H5N1 and what people in China see with their own eyes. Many reports of total H5N1 cases exclude China due to widespread disbelief in China's official numbers.

2004

In January 2004 a major new outbreak of H5N1 surfaced in Vietnam and Thailand's poultry industry, and within weeks spread to ten countries and regions in Asia, including Indonesia, South Korea, Japan and China. In October 2004 researchers discovered H5N1 is far more dangerous than previously believed because waterfowl, especially ducks, were directly spreading the highly pathogenic strain of H5N1 to chickens, crows, pigeons, and other birds and that it was increasing its ability to infect mammals as well. From this point on, avian influenza experts increasingly refer to containment as a strategy that can delay but not prevent a future avian flu pandemic.

2005



The spread of avian influenza in the eastern hemisphere

In January 2005 an outbreak of avian influenza affected thirty three out of sixty four cities and provinces in Vietnam, leading to the forced killing of nearly 1.2 million poultry. Up to 140 million birds are believed to have died or been killed because of the outbreak. In April 2005 there begins an unprecedented die-off of over 6,000 migratory birds at Qinghai Lake in central China over three months. This strain of H5N1 is the same strain as is spread west by migratory birds over at least the next ten months. In August 2005 H5N1 spread to Kazakhstan, Mongolia and Russia. On September 29, 2005, David Nabarro, the newly appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill 5 to 150 million people. David Nabarro later stated that as the virus had spread to migratory birds, an outbreak could start in Africa or the Middle East. Later in 2005 H5N1 spread to Turkey, Romania, Croatia and Kuwait.

2006

- In the first two months of 2006 H5N1 spread to other Asian countries (such as India), north Africa, and Europe in wild bird populations possibly signaling the beginning of H5N1 being endemic in wild migratory bird populations on multiple

continents for decades, permanently changing the way poultry are farmed. In addition, the spread of highly pathogenic H5N1 to wild birds, birds in zoos and even sometimes to mammals (example: pet cats) raises many unanswered questions concerning best practices for threat mitigation, trying to balance reducing risks of human and nonhuman deaths from the current nonpandemic strain with reducing possible pandemic deaths by limiting its chances of mutating into a pandemic strain. Not using vaccines can result in the need to kill significant numbers of farm and zoo birds, while using vaccines can increase the chance of a flu pandemic.

- By April 2006 scientists had concluded that containment had failed due to the role of wild birds in transmitting the virus and were now emphasizing far more comprehensive risk mitigation and management measures.
- In June 2006 WHO predicted an upsurge in human deaths due to H5N1 during late 2006 or early 2007 following a summer/fall lull in most countries, as H5N1 appears to be somewhat seasonal in nature. In July and August 2006 significantly increased numbers of bird deaths due to H5N1 were recorded in Cambodia, China, Laos, Nigeria, and Thailand while continuing unabated a rate unparalleled in Indonesia.
- In September, Egypt and Sudan joined the list of nations seeing a resurgence of bird deaths due to H5N1.
- In November and December, South Korea and Vietnam joined the list of nations seeing a resurgence of bird deaths due to H5N1.

2007

In January, Japan, Hungary, Russia, and the United Kingdom joined the list of nations seeing a resurgence of bird deaths due to H5N1. In February, Pakistan, Turkey, Afghanistan, and Myanmar joined the list and Kuwait saw its first major outbreak of H5N1 avian influenza.

In March Bangladesh and Saudi Arabia each saw their first major outbreak of H5N1 avian influenza and Ghana in May.

As H5N1 continued killing many birds and a few people throughout the spring in countries where it is now endemic, in June Malaysia and Germany saw a resurgence of bird deaths due to H5N1, while the Czech Republic and Togo experienced their first major outbreak of H5N1 avian influenza.

In July France and India also saw a resurgence of bird deaths due to H5N1.

2008

January

- January 24, 2008: China's health ministry has confirmed a 22-year-old man has died from H5N1 in central Hunan province.

February

- February 26, 2008: H5N1 killed a school teacher from northern Vietnam in the country's 51st death from the disease, and health officials fretted that the virus would spread further.
- February 28, 2008: There are no indications that H5N1 is becoming a bigger problem in China despite the deaths of three people from the disease this year, the World Health Organisation said Wednesday.

March

- March 4, 2008: H5N1 virus confirmed as the cause of death for a 25 year old female from Sennoris District, Fayum Governorate, Egypt.

June

- June 7, 2008: Hong Kong found the H5N1 bird flu virus at a poultry stall in Sham Shui Po. 2,700 birds were ordered to be killed by the local government. A new regulation requires all live chickens not sold by 8pm to be killed. The chairman of the Hong Kong Poultry Wholesalers Association said the government's decision makes it very difficult for their business to continue. Retailers who keep live poultry after 8pm are now subject to a fine of HK\$50,000 and six months imprisonment.

July

As of the July 25, 2008 FAO Avian Influenza Disease Emergency Situation Update, H5N1 pathogenicity is continuing to gradually rise in wild birds in endemic areas but the avian influenza disease situation in farmed birds is being held in check by vaccination. Eleven outbreaks of H5N1 were reported worldwide in June 2008 in five countries (China, Egypt, Indonesia, Pakistan and Vietnam) compared to 65 outbreaks in June 2006 and 55 in June 2007. The "global HPAI situation can be said to have improved markedly in the first half of 2008 [but] cases of HPAI are still underestimated and underreported in many countries because of limitations in country disease surveillance systems".

2009

January

- January 16, 2009: H5N1 hits Nepal for first time. In a Jan 16 report to the World Organization for Animal Health (OIE), government officials in Nepal said the virus struck backyard poultry in a village in Jhapa district in the southeastern corner of Nepal. Though the Nepal Government announced that bird flu in the country's Kakarbhitta area is under control, avian virus surfaced again in Sharanamati of Jhapa district. Over 150 chickens died in the Indian border town, 35 km southwest of Kakarbhitta. The Ministry of Agriculture and Cooperatives

declared the area surrounding Sharanamati a "bird-flu affected area" and increased surveillance along the border. A Rapid Response Team (RRT) was dispatched to control the virus. The government also banned the transportation of poultry products throughout the country. The first outbreak was confirmed in Kakarbhitta on January 16. 28,000 chickens were killed in the area to control the virus. Earlier, Agriculture Minister Jayprakash Gupta asked the international community and donor agencies to provide help to Nepal fight the disease. The Indo-Nepal border was in heightened alert because of the disease.

February

- February 21, 2009: H5N1 killed a 23-year-old woman named Lý Tài Múi from Nà Cánh, Quảng An, Đầm hà, Quảng Ninh, Vietnam.
- February 25, 2009: H5N1 virus confirmed as the cause of death for a 32-year-old man from Quang Binh, Vietnam.

March

- March 19, 2009: H5N1 virus confirmed as the cause of death for a 3 year old boy from Đồng Tháp, Vietnam.
- March 21, 2009: state media reported H5N1 might be the cause of a death of a female in Bạc Liêu, Vietnam.

April

- April 24, 2009: H5N1 virus confirmed as the cause of death for a 23-year-old woman from Thanh Hoa, Vietnam.

June

- July 1, 2009: 3 cases of H5N1 were confirmed in Egypt. All 3 recovered.

Pig cases



Pigs can harbor influenza viruses adapted to humans and others that are adapted to birds, allowing the viruses to exchange genes and create a pandemic strain.

Avian influenza virus H3N2 is endemic in pigs ("swine flu") in China and has been detected in pigs in Vietnam, increasing fears of the emergence of new variant strains. Health experts say pigs can carry human influenza viruses, which can combine (i.e. exchange homologous genome sub-units by genetic reassortment) with H5N1, passing genes and mutating into a form which can pass easily among humans. H3N2 evolved from H2N2 by antigenic shift and caused the Hong Kong Flu pandemic of 1968 and 1969 that killed up to 750,000 humans. The dominant strain of annual flu in humans in January 2006 is H3N2. Measured resistance to the standard antiviral drugs amantadine and rimantadine in H3N2 in humans has increased to 91% in 2005. A combination of these two subtypes of the species known as the avian influenza virus in a country like China is a worst case scenario. In August 2004, researchers in China found H5N1 in pigs.

In 2005 it was discovered that H5N1 "could be infecting up to half of the pig population in some areas of Indonesia, but without causing symptoms [...] Chairul Nidom, a virologist at Airlangga University's tropical disease center in Surabaya, Java, was conducting independent research earlier this year. He tested the blood of 10 apparently healthy pigs housed near poultry farms in western Java where avian flu had broken out, *Nature* reported. Five of the pig samples contained the H5N1 virus. The Indonesian government has since found similar results in the same region, *Nature* reported. Additional tests of 150 pigs outside the area were negative."

Felidae (cats)



Domestic cats can get H5N1 from eating birds, and can transmit it to other cats and possibly to people.

"In Bangkok, Thailand, all the cats in one household are known to have died of H5N1 in 2004. Tigers and leopards in Thai zoos also died, while in 2007 two cats near an outbreak in poultry and people in Iraq were confirmed to have died of H5N1, as were three German cats that ate wild birds. In Austria cats were infected but remained healthy". Cats in Indonesia were also found to have been infected with H5N1.

The spread to more and more types and populations of birds and the ability of felidae (cats) to catch H5N1 from eating this natural prey means the creation of a reservoir for

H5N1 in cats where the virus can adapt to mammals is one of the many possible pathways to a pandemic.

October 2004

Variants have been found in a number of domestic cats, leopards and tigers in Thailand, with high lethality. "The Thailand Zoo tiger outbreak killed more than 140 tigers, causing health officials to make the decision to cull all the sick tigers in an effort to stop the zoo from becoming a reservoir for H5N1 influenza. A study of domestic cats showed H5N1 virus infection by ingestion of infected poultry and also by contact with other infected cats (Kuiken et al., 2004)." The initial OIE report reads: "the clinical manifestations began on 11 October 2004 with weakness, lethargy, respiratory distress and high fever (about 41-42 degrees Celsius). There was no response to any antibiotic treatment. Death occurred within three days following the onset of clinical signs with severe pulmonary lesions."

February 28, 2006

A dead cat infected with the H5N1 bird flu virus was found in Germany.

March 6, 2006

Hans Seitinger, the top agriculture official in the southern state of Styria, Austria announced that several still living cats in Styria have tested positive for H5N1:

August 2006

It was announced in the August 2006 CDC EID journal that while literature describing HPAI H5N1 infection in cats had been limited to a subset of clade I viruses; a Qinghai-like virus (they are genetically distinct from other clade II viruses) killed up to five cats and 51 chickens from February 3 to February 5, 2006 in Grd Jotyar (~10 km north of Erbil City, Iraq). Two of the cats were available for examination.

"An influenza A H5 virus was present in multiple organs in all species from the outbreak site in Grd Jotyar (Table). cDNA for sequencing was amplified directly from RNA extracts from pathologic materials without virus isolation. On the basis of sequence analysis of the full HA1 gene and 219 amino acids of the HA2 gene, the viruses from the goose and 1 cat from Grd Jotyar and from the person who died from Sarcapcarn (sequence derived from PCR amplification from first-passage egg material) are >99% identical at the nucleotide and amino acid levels (GenBank nos. DQ435200–02). Thus, no indication of virus adaptation to cats was found. The viruses from Iraq are most closely related to currently circulating Qinghai-like viruses, but when compared with A/bar-headed goose/Qinghai/65/2005 (H5N1) (GenBank no. DQ095622), they share only 97.4% identity at the nucleic acid level with 3 amino acid substitutions of unknown significance. On the other hand, the virus from the cat is only 93.4%

identical to A/tiger/Thailand/CU-T4/2004(H5N1) (GenBank no. AY972539). These results are not surprising, given that these strains are representative of different clades (8,9). Sequencing of 1,349 bp of the N gene from cat 1 and the goose (to be submitted to GenBank) show identity at the amino acid level, and that the N genes of viruses infecting the cat and goose are >99% identical to that of A/bar-headed goose/Qinghai/65/2005(H5N1). These findings support the notion that cats may be broadly susceptible to circulating H5N1 viruses and thus may play a role in reassortment, antigenic drift, and transmission."

January 24, 2007

"Chairul Anwar Nidom of Airlangga University in Surabaya, Indonesia, told journalists last week that he had taken blood samples from 500 stray cats near poultry markets in four areas of Java, including the capital, Jakarta, and one area in Sumatra, all of which have recently had outbreaks of H5N1 in poultry and people. Of these cats, 20% carried antibodies to H5N1. This does not mean that they were still carrying the virus, only that they had been infected - probably through eating birds that had H5N1. Many other cats that were infected are likely to have died from the resulting illness, so many more than 20% of the original cat populations may have acquired H5N1."

Mammals in general



Martens and an unknown number of other mammals can catch H5N1, illustrating the unprecedented ability of H5N1 to survive and spread.

H5N1 has been transmitted in laboratories to many species including mice and ferrets to study its effects.

H5N1 was transmitted in the wild to three civet cats in Vietnam in August 2005 and a stone marten in Germany in March 2006.

The BBC reported that a stray dog in Azerbaijan died from the disease on March 15, 2006.

People living in areas where the A(H5N1) virus has infected birds are advised to keep their cats indoors. "Cats can be infected through the respiratory tract. Cats can also be infected when they ingest the virus, which is a novel route for influenza transmission in mammals. But cats excrete only one-thousandth the amount of virus that chickens do [...]. The concern is that if large numbers of felines and other carnivores become infected, the virus might mutate in a series of events that could lead to an epidemic among humans. Dogs, foxes, seals and other carnivores may be vulnerable to A(H5N1) virus infection, Dr. Osterhaus said. Tests in Thailand have shown that the virus has infected dogs without causing apparent symptoms."

H5N1 has the potential to infect cattle. Asymptomatic shedding of H5N1 by infected calves and subsequent seroconversion is possible. Bird-to-calf transmission resulting in seroconversion is probable. While the incidence of clinical infections of cattle with H5N1 in H5N1 endemic regions should be low, "serum from bovine species would be a valuable source of additional information about transmission events, especially in regions like Asia and Egypt, where HPAIV (H5N1) is endemic and probability of contact between poultry and cattle is high."

Chapter 12

Global Spread of H5N1 in 2004 & 2005

Global spread of H5N1 in 2004

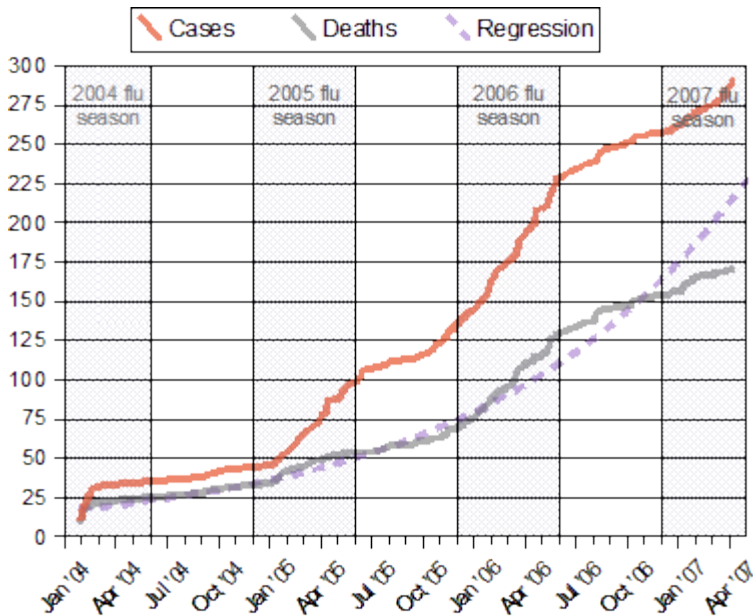
The **global spread of (highly pathogenic) H5N1** in birds is considered a significant pandemic threat.

While prior H5N1 strains have been known, they were significantly different from the current H5N1 strain on a genetic level, making the global spread of this new strain unprecedented. The current H5N1 strain is a fast-mutating, highly pathogenic avian influenza virus (HPAI) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species especially over a wide area).

H5N1 caused flu outbreaks in 1959 and in 1991 but these strains were very different from the current highly pathogenic strain of H5N1. Evolution from 1999 to 2002 created the Z genotype which became the dominant strain of highly pathogenic H5N1 in 2004.

In January 2004 a major new outbreak of H5N1 surfaced in Vietnam and Thailand's poultry industry, and within weeks spread to ten countries and regions in Asia, including Indonesia, South Korea, Japan and China. In October 2004 researchers discovered H5N1 is far more dangerous than previously believed because waterfowl were directly spreading the highly pathogenic strain of H5N1 to chickens, crows, pigeons, and other birds and that it was increasing its ability to infect mammals as well. From this point on, avian influenza experts increasingly refer to containment as a strategy that can delay but not prevent a future avian flu pandemic.

Cumulative Human Cases of and Deaths from H5N1 As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007." Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

January

- A major new outbreak of H5N1 surfaced in Vietnam and Thailand's poultry industry, and within weeks spread to ten countries and regions in Asia, including Indonesia, South Korea, Japan and China. Intensive efforts were undertaken to slaughter chickens, ducks and geese (over forty million chickens alone were slaughtered in high-infection areas), and the outbreak was contained by March, but the total human death toll in Vietnam and Thailand was twenty three people.

February

- "The Ministry of Public Health in Thailand has confirmed the country's tenth case of H5N1 infection."

July

- Fresh outbreaks in poultry were confirmed in Ayutthaya and Pathumthani provinces of Thailand, and Chaohu city in Anhui, China. Research identifies the dominant strain of H5N1 as the "Z genotype".

August

- Avian flu was confirmed in Kampung Pasir, Kelantan, Malaysia. Two chickens were confirmed to be carrying H5N1. As a result Singapore has imposed a ban on the importation of chickens and poultry products. Similarly the EU has imposed a ban on Malaysian poultry products. A cull of all poultry has been ordered by the Malaysian government within a 10 km radius of the location of this outbreak. These moves appear to have been successful and since then, Singapore has lifted the ban and Malaysia has requested the OIE declare Malaysian poultry bird flu free.

September

- More cases of H5N1 in humans in Thailand.

October

- **Researchers discover H5N1 is far more dangerous than previously believed.** "In the past, outbreaks of highly pathogenic avian influenza in poultry began following the primary introduction of a virus, of low pathogenicity, probably carried by a wild bird. The virus then required several months of circulation in domestic poultry in order to mutate from a form causing very mild disease to a form causing highly pathogenic disease, with a mortality approaching 100%. Only viruses of the H5 and H7 subtypes are capable of mutating to cause highly pathogenic disease. In the present outbreaks, however, asymptomatic domestic ducks can directly introduce the virus, in its highly pathogenic form, to poultry flocks." Limiting this conclusion to domestic waterfowl proved to be wishful thinking, as in later months it became clear that nondomestic waterfowl were also directly spreading the highly pathogenic strain of H5N1 to chickens, crows, pigeons, and other birds and that it was increasing its ability to infect mammals as well. From this point on, avian influenza experts increasingly refer to containment as a strategy that can delay but not prevent a future avian flu pandemic.

November

- The U.S.'s National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases's (NIAID) Influenza Genome Sequencing Project to provide complete sequence data for selected human and avian influenza isolates begins.

December

- "[F]irst human case of H5N1 [is] detected in Viet Nam since early September".

Global spread of H5N1 in 2005

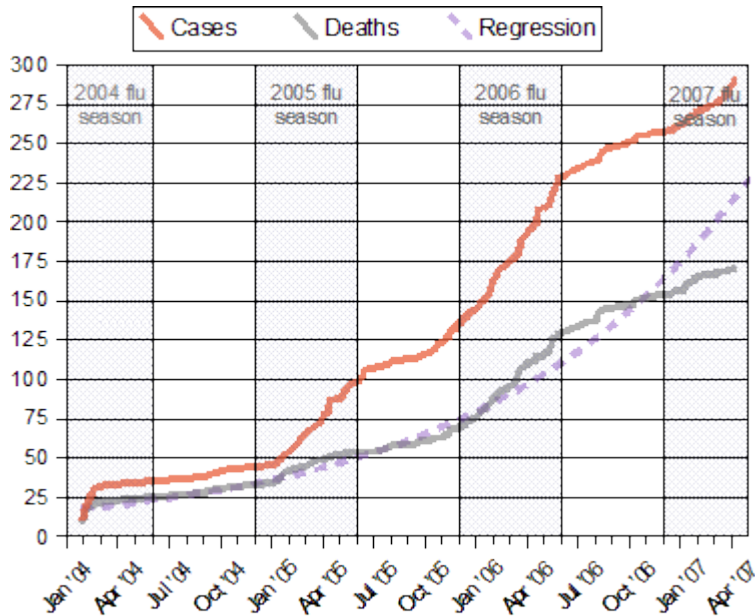
The **global spread of (highly pathogenic) H5N1** in birds is considered a significant pandemic threat.

While prior H5N1 strains have been known, they were significantly different from the current H5N1 strain on a genetic level, making the global spread of this new strain unprecedented. The current H5N1 strain is a fast-mutating, highly pathogenic avian influenza virus (HPAI) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species especially over a wide area).

In January 2005 an outbreak of avian influenza affected thirty three out of sixty four cities and provinces in Vietnam, leading to the forced killing of nearly 1.2 million poultry. Up to 140 million birds are believed to have died or been killed because of the outbreak. In April 2005 an unprecedented die-off began of over 6,000 migratory birds at Qinghai Lake in central China over three months. This strain of H5N1 is the same strain as is spread west by migratory birds over at least the next ten months. In August 2005 H5N1 spread to Kazakhstan, Mongolia and Russia. On September 29, 2005, David Nabarro, the newly appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill 5 to 150 million people. David Nabarro later stated that as the virus had spread to migratory birds, an outbreak could start in Africa or the Middle East. Later in 2005 H5N1 spread to Turkey, Romania, Croatia and Kuwait.

Cumulative Human Cases of and Deaths from H5N1

As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007."
Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

January

- An outbreak of avian influenza affected thirty three out of sixty four cities and provinces in Vietnam, leading to the forced killing of nearly 1.2 million poultry. Up to 140 million birds are believed to have died or been killed because of the outbreak.

February

- "Surveillance stepped up in province where Cambodia's first human avian influenza case was detected".

March

- Vietnam and Thailand have seen several isolated cases where human-to-human transmission of the virus has been suspected in care-givers of H5N1 patients, including a mother of a girl who died from H5N1 and two nurses.

April

- "The Ministry of Health in Vietnam has provided WHO with official confirmation of an additional eight human cases of H5N1 avian influenza. Two of the cases were recently detected, between 2 and 8 April, in Hung Yen and Ha Tay Provinces, respectively. Both patients are alive. The other six cases are thought to have been detected prior to 2 April. WHO is seeking further details from the authorities on this six cases."
- There is an unprecedented die-off of over 6,000 migratory birds at Qinghai Lake in central China during April, May and June. This strain of H5N1 is the same strain as is spread west by migratory birds over at least the next ten months. "The RNA sequence of the Qinghai virus reveals that three of its eight genes are almost identical to those of a virus isolated from a chicken in Shantou in 2003. The other five genes resemble those of viruses found in southern China earlier in 2005, which belong to the "Z genotype" virus circulating across east Asia."

May

- "Since January 2004, when human cases of H5N1 avian influenza were first reported in the current outbreak, 97 cases and 53 deaths have been reported in Vietnam, Thailand and Cambodia. Vietnam, with 76 cases and 37 deaths, has been the most severely affected country, followed by Thailand, with 17 cases and 12 deaths, and Cambodia, with 4 cases and 4 deaths."

June

- "[T]esting of clinical specimens by international experts working in Vietnam provided further suggestive evidence of more widespread infection with the virus, raising the possibility of community-acquired infection" but "the detection of H5N1 in clinical specimens is technically challenging and prone to errors" so team members and supplies from "institutes in Australia, Canada, Hong Kong SAR, Japan, the United Kingdom, and the United States of America having extensive experience in the testing of avian influenza viruses in human clinical specimens" investigated and concluded that "no laboratory evidence suggesting that human infections are occurring with greater frequency or that the virus is spreading readily among humans."

July

- A death in Jakarta was the first confirmed human fatality in Indonesia.
- On July 28, avian influenza was reported to have killed two more people in Vietnam, raising the death toll to sixty.

August

August 3, 2005

- WHO said it was following closely reports from China that at least 38 people have died and more than 200 others have been made ill by a swine-borne virus in Sichuan Province. Sichuan Province, where infections with *Streptococcus suis* have been detected in pigs in a concurrent outbreak, has one of the largest pig populations in China. The outbreak in humans has some unusual features and is being closely followed by the WHO.

August 11, 2005

- An avian outbreak of H5N1 flu was confirmed in Kazakhstan and Mongolia, suggesting further spread of the virus.

August 22, 2005

- The virus was found in western Russia, marking its appearance in Europe. As a result, Dutch authorities ordered that free-range chickens would have to be kept indoors. EU officials chose not to impose a similar policy on member countries.

September

September 29, 2005

- David Nabarro, the newly appointed Senior United Nations System Coordinator for Avian and Human Influenza, warned the world that an outbreak of avian influenza could kill 5 to 150 million people. Also, due to a bipartisan effort of the United States Senate, \$4 billion dollars was appropriated to develop vaccines and treatments for Avian influenza. David Nabarro stated that as the virus had spread to migratory birds, an outbreak could start in Africa or the Middle East.
- Agricultural ministers of Association of South East Asian Nations announced a three-year plan to counter the spread of the disease.

October

October 13, 2005

- The EU Health Commissioner Markos Kyprianou confirmed that tests on the dead turkeys found on farms in Kiziksa, Turkey, showed that they had died from the H5N1 strain. Even before the test results were available, some 5,000 birds and poultry have been culled in the area. It is believed that the disease had spread from migratory birds that land at the Manyas bird sanctuary (a few miles from the infected farm) on their way to Africa.

October 15, 2005

- The British Veterinary Laboratory in Weybridge confirmed that the virus detected in Ciamurlia, Romania is H5N1.

October 19, 2005

- China announced a fresh outbreak of bird flu, saying 2,600 birds have died from the disease in Inner Mongolia. The deaths, at a farm near the region's capital of Hohhot, were due to the H5N1 strain, the Xinhua news agency said.

October 26, 2005

- Croatia announced H5N1 strain was found in dead swans.

October 31, 2005

- Russia confirmed previously suspected H5N1 bird flu in ten rural communities across Russia. The confirmed outbreak sites are in the central areas of Tula and Tambov, as well as in the Urals province of Chelyabinsk and in Omsk and Altai, in Siberia.

November

November 12, 2005

- Kuwait has reported positive testing of two birds, one infected with H5N1, and the other with the H5N2 virus, making them the first cases of infection in the Middle East. A flamingo holding the H5N1 virus was found dead by the sea, as Gulf News reports, it was killed by authorities and did not die from the virus.

December

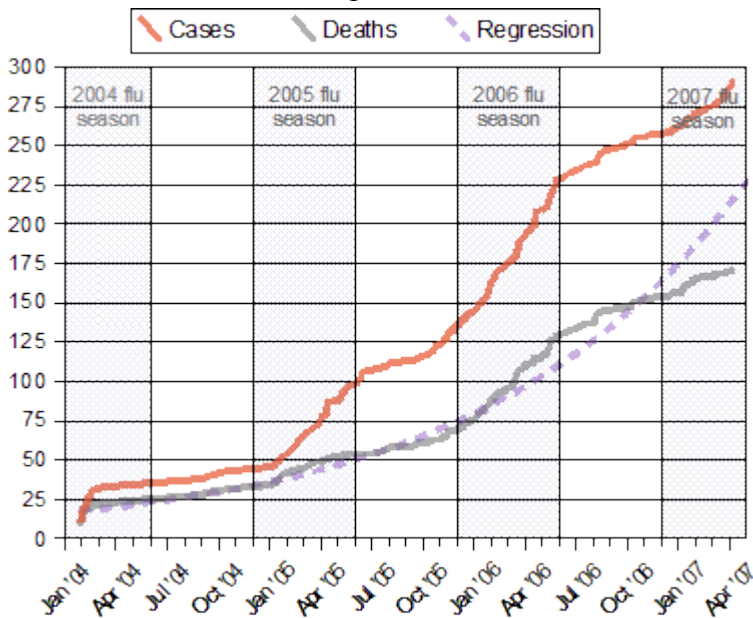
December 30, 2005 "China confirms its third human death from bird flu. That brings the death toll [...] to 74, comprising 14 victims in Thailand, four in Cambodia, 11 in Indonesia, 42 in Vietnam and three in China."

Chapter 13

Global Spread of H5N1 in 2006

Cumulative Human Cases of and Deaths from H5N1

As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007." Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

The **global spread of (highly pathogenic) H5N1** in birds is considered a significant pandemic threat.

While prior H5N1 strains have been known, they were significantly different from the current H5N1 strain on a genetic level, making the global spread of this new strain unprecedented. The current H5N1 strain is a fast-mutating, highly pathogenic avian

influenza virus (HPAI) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species especially over a wide area).

In the first two months of 2006 H5N1 spread to Africa and Europe in wild bird populations possibly signaling the beginning of H5N1 being endemic in wild migratory bird populations on multiple continents for decades, permanently changing the way poultry are farmed. In addition, the spread of highly pathogenic H5N1 to wild birds, birds in zoos and even sometimes to mammals (example: pet cats) raises many unanswered questions concerning best practices for threat mitigation, trying to balance reducing risks of human and nonhuman deaths from the current nonpandemic strain with reducing possible pandemic deaths by limiting its chances of mutating into a pandemic strain. Not using vaccines can result in the need to kill significant numbers of farm and zoo birds, while using vaccines can increase the chance of a pandemic.

By April 2006 scientists had concluded that containment had failed due to the role of wild birds in transmitting the virus and were now emphasizing far more comprehensive risk mitigation and management measures.

In June 2006 WHO predicted an upsurge in human deaths due to H5N1 during late 2006 or early 2007. In July and August 2006 significantly increased numbers of bird deaths due to H5N1 were recorded in Cambodia, China, Laos, Nigeria, and Thailand while continuing unabated a rate unparalleled in Indonesia. In September, Egypt and Sudan joined the list of nations seeing a resurgence of bird deaths due to H5N1; followed by Vietnam and South Korea in December.

January

January 5, 2006

- A second Turkish child from the same family died from bird flu on Thursday at a hospital in eastern Turkey, where she was being treated, a regional governor said. Her brother, 14-year-old Mehmet Ali Kocyigit, had already died of the H5N1 strain of bird flu, officials said on Wednesday, confirming the first human death from the disease outside China and southeast Asia. "We lost Fatma Kocyigit this morning", Niyazi Tanilir, governor in the eastern province of Van, said on the CNN Turk news channel. Newspapers said Fatma was 15 years old. She died around 6:30 a.m. (0430 GMT).

January 7, 2006

- Two more children in Turkey are hospitalized after contracting bird flu like symptoms then later test positive for H5N1. They are both from the same area as the prior three children that died from H5N1 bringing the total number of cases in Turkey to 5, with 2 of them fatal. 76 people have died since the outbreak began in 2003.

January 8, 2006

- Three people are hospitalized after developing suspected H5N1 in the Turkish capital.

January 10, 2006

- A woman is diagnosed with bird flu, as Turkey struggles to contain the outbreak.
- China announces that two more people had died of bird flu before 2006 began.
- Indonesia confirms that a 29 year old woman has died from suspected bird flu.
- Birds begin dying in Nigeria. It is not known until February that it is an H5N1 outbreak.

January 16, 2006

- A 15-year-old Indonesian girl from Indramayu, Java, dies of bird flu.

January 18, 2006

- China and Turkey each confirm another human death from H5N1.
- A 13-year-old boy dies in Indonesia, he is the brother of the girl who died on January 16.
- Donor nations pledge 1850 million US dollars to combat bird flu at the two day International Pledging Conference on Avian and Human Influenza held in China.

January 21, 2006

- The WHO confirms that the two Indonesian children died of H5N1.

January 29, 2006

- H5N1 is found in dead birds in northern Cyprus. The European Commission freezes transfers of animals and animal products from the north of the island through the green line to the areas controlled by the Republic of Cyprus and to the rest of the European Union.

January 30, 2006

- According to WHO:

The Ministry of Health in Iraq has confirmed the country's first case of human infection with the H5N1 avian influenza virus. The case occurred in a 15-year-old girl who died on 17 January following a severe respiratory illness. Her symptoms were compatible with a diagnosis of H5N1 avian influenza. Preliminary laboratory confirmation was provided by a US Naval Medical Research Unit located in Cairo, Egypt. The girl's 39-year-old uncle, who cared for her during her

illness, developed symptoms on 24 January and died of a severe respiratory disease on 27 January. Both patients resided in the town of Raniya near Sulaimaniyah in the northern part of the country, close to the border with Turkey. Poultry deaths were recently reported in their neighbourhood, but H5N1 avian influenza has not yet been confirmed in birds in any part of the country. Poultry samples have been sent for testing at an external laboratory. A history of exposure to diseased birds has been found for the girl. The uncle's source of infection is under investigation. The Ministry of Health has further informed WHO of a third human case of respiratory illness that is under investigation for possible H5N1 infection. The patient is a 54-year-old woman, from the same area, who was hospitalized on 18 January. Specimens are on their way to a WHO collaborating laboratory in the United Kingdom for diagnostic confirmation and further analysis. An international team, including representatives of other UN agencies, is being assembled to assist the Ministry of Health in its investigation of the situation and its planning of an appropriate public health response. WHO staff within Iraq have been directly supporting the government's operational response, which was launched shortly after the girl's death. Iraq is the seventh country to report human H5N1 infection in the current outbreak. The first human case occurred in Viet Nam in December 2003.

February

February 4, 2006

- Indonesia confirms three new cases, two of which were fatal.
- A dead swan near the city of Vidin, Bulgaria is found to contain the H5 strain. Further testing begins to determine if the bird died from the H5N1 type of the disease. Over 20 dead birds are found along the Danube and in lakes near the Black Sea.

February 6, 2006

- Preliminary report is sent from Nigeria to OIE on a massive bird die off that began January 10. Report was sent by Dr. Junaidu A. Maina, Acting Director, Department of Livestock and Pest Control Services, Federal Ministry of Agriculture and Rural Development, Abuja, Nigeria.

February 7, 2006

- OIE/FAO Reference Laboratory for avian influenza and Newcastle disease in Padova, Italy, confirmed highly pathogenic avian influenza virus subtype H5N1 in Nigerian isolates from samples taken January 16.

February 8, 2006

- The Nigeria situation is announced to the world. Nigeria is the first African country to have an H5N1 outbreak confirmed. It affected a commercial chicken farm (owned by Nigeria's sports minister, Saidu Samaila Sambawa) in which ostriches and geese were also kept, in Jaji village in Igabi administrative division (local government area or LGA) in Kaduna State in Nigeria. The control measures said to be used include killing poultry, quarantining poultry, poultry movement control, and disinfection; however there are complaints that these measures are in fact not being carried out. 40,000 out of 46,000 caged chickens died of H5N1 despite being treated by their owner with broadspectrum antibiotics. The remaining 6,000 have been killed to try to control spread of the disease.

February 9, 2006

- Four new farms in Nigeria are confirmed to have H5N1 outbreaks: two in Kano State, one in Plateau State and a second farm in Kaduna State.
- Veterinarians from Onderstepoort Veterinary Institute, Faculty of Veterinary Science, University of Pretoria in South Africa offer their expertise to assist in tracking occurrence of the virus in Nigeria and elsewhere in Africa.
- The United States, OIE and WHO are sending experts, supplies and money to Nigeria to help with this H5N1 crisis.
- H5N1 flu in Africa is expected to spread and create a very severe situation.
- Farmers in northern Nigeria are rushing to sell dead chickens at cut-price rates before government bans are put into place. Promised measures to contain the disease are still not in place.
- European countries are facing an increased probability that spring bird migrations from Africa will bring H5N1.
- Countries in Africa near to Nigeria are responding with "dread" and import restrictions.

February 10, 2006

- Officials in Azerbaijan say H5N1 virus has been identified in wild birds floating dead in the Caspian Sea near Baku

February 11, 2006

- The government of Italy confirms that H5N1 has been found in wild swans in Sicily and elsewhere in the country. It is also found in wild birds in Greece and Bulgaria.

February 12, 2006

- The government of Slovenia confirms that the virus subtype H5 has been found in a wild swan by the Drava river near Maribor. The samples have been sent to the United Kingdom to determine if it is the deadly H5N1 strain.

February 13, 2006

- Nihat Kabil, Bulgaria's Minister of Agriculture and Forestry, confirms a second case of a swan with the H5 virus. While the first case was in Vidin (in the country's northwest), the second one was near Krajmorie, a Black Sea port in the Burgas region (in the country's southeast), about 3.5 km (2 mi) from an egg farm. Several other cases have been reported in other parts of the country, and Mr. Kabil has said that there is a high probability that Bulgaria will have its first mass case within days.

February 14, 2006

- Health authorities report the first case of the H5N1 virus in Austria. Two dead swans at Mellach near Graz were found to be carrying the virus.
- Following the discovery of four dead swans suspected of carrying the H5N1 virus on the island of Rügen in North-east Germany, authorities in Germany and several other EU countries make it compulsory for all poultry to be kept inside enclosures effective as of February 20.

February 15, 2006

- Slovenian Ministry of Agriculture, Forestry and Food declares entire Slovenia a bird-flu high risk zone after tests confirmed the dead swan (found on 9 February) was carrying H5. It is sent to Great Britain for further subtype determination.
- Avian influenza H5N1 is identified in some dead swans in Hungary. Not known until the end of February whether they carried the human-infecting strain (genotype Z) of H5N1.
- Iran reports cases in wild birds.

February 17, 2006

- The presence of H5N1 in Slovenia is confirmed.
- Egypt has detected its first cases in several parts of the country, the government detailed three separate sites where birds were found carrying the virus.
- France has recorded a case of a duck infected with the H5 virus in Ain, near Lyon. It was later confirmed that the duck was infected with the H5N1 strain of the virus. A swan earlier tested negative for the disease.
- Iraq confirms a second person has died of H5N1 - he was the uncle of the country's initial death.

February 18, 2006

- Officials in India's western Maharashtra state are planning a poultry cull after the country reported its first cases of the deadly H5N1 strain of bird flu.

February 19, 2006

- First suspected bird flu human death reported from Surat, Gujarat, India.

February 20, 2006

- Croatia has recorded a new case of a swan infected with the H5 virus in C(iovu, near Trogir. In the same time, H5 is confirmed in dead swan found in Jajce, Bosnia and Herzegovina.
- A United Kingdom laboratory confirms the three cases of H5N1 in dead swans found near the cities of Dobrich, Varna and Burgas, in Bulgaria's northeastern and southeastern regions. The previous H5N1 case was recorded near Vidin in the northwest.

February 21, 2006

- The Malaysian government confirms 40 chickens died of H5N1 in Selangor.
- Croatia confirmed the previous day's case to be H5N1.
- Professor Neil Ferguson, Imperial College London biologist, says:

"This is a disease which doesn't go away so we are going to be living with H5N1 in Western Europe, I believe, in wild bird populations - even endemic in wild bird populations - for decades perhaps, or even sporadically in those populations every year."

- The respected science journal Nature says:

"The virus is highly likely to become endemic, says Peter Openshaw, head of the respiratory viral infections section at the National Heart and Lung Institute in London, UK. We have to change the way poultry are farmed. [...] Jan Slingenbergh, an animal health expert at the United Nation's Food and Agriculture Organization (FAO) in Rome, Italy, points out that H5N1 may survive in icy lake waters over European winters, potentially infecting any migratory birds that subsequently arrive. The virus could also become established in permanently resident European birds; Openshaw notes that H5N1 has so far been able to infect a wide range of species. If this happens, farming practices will have to be changed, says Neil Ferguson, an epidemiologist at Imperial College London, UK, who is advising the British government on how to deal with possible future outbreaks."

February 23, 2006

- Slovakia has become the latest EU nation to confirm cases of the virulent H5N1 bird flu strain. One of the dead birds was found in the capital, Bratislava, the other in Gabčíkovo, southwestern Slovakia

February 25, 2006

- France For the first time a EU farm becomes infected and 80% of the more than 11 thousand birds die for the H5N1 flu in the previous week

February 27, 2006

- Niger confirms a case of H5N1 bird flu in a flock of ducks near the border with Nigeria
- Switzerland says a dead swan has been found on Lake Geneva which the H5 virus.
- Bosnia's veterinary office said that tests at the European Union reference laboratory confirmed its first case of the deadly H5N1 bird flu virus in two wild swans near Jajce. Thousands of birds were culled.

February 28, 2006

- Confirmed case of highly pathogenic H5 in Sweden
- Finland: The 20 dead ducks and 1 crow at Kotka, Sapokka park, were confirmed not to be carriers of H5N1. The reason for the deaths remains to be solved. On March 13 an insecticide, parathion was confirmed to be the reason for deaths. The toxin is life-threatening to humans. The use of parathion has been banned in Finland since 1992.

March

March 1, 2006

- Scientists confirm the dead swan found on Lake Geneva on February 27 had H5N1. It is the first confirmed case of H5N1 in Switzerland.
- A second case of H5 bird flu has been found in Switzerland, this time on Lake Constance, near the town of Egnach, Thurgau.
- Greece confirms three new cases of H5N1 in swans found the northern part of the country, bringing the total number of cases in the country to 19.
- 8 Quebec farms are quarantined after receiving live poultry from France. The province braces itself for its first H5N1 cases.

March 2, 2006

- A chicken from a farm, 175 km south from Addis Ababa, is being tested for the possibility of having H5N1 in Ethiopia, the first possible case in East Africa.
- Serbia detected the bird flu in a dead swan that was found in northwest Serbia (near Croatia)
- Tests on live ducks imported France to Quebec have come back negative for H5N1.

March 3, 2006

- Sweden confirms eight new cases of H5 bird flu virus
- Azerbaijan confirms first case of H5N1 bird flu in poultry

March 4, 2006

- H5N1 was found in a wild goose near Lüneburg, Lower Saxony, Germany, making it the sixth federal state in the country to report a case of the disease.
- Austria's cases of H5N1 rise to 29 with three ducks, a seagull, and a grebe found with the disease in Vorarlberg.

March 5, 2006

- Poland has reported its first case of H5N1 in a wild swan found dead two days ago in Toruń, a city in northern Poland.
- A man in the southern Chinese province of Guangdong has died of H5N1. This is the eighth death in the country caused by avian flu.
- A new case of H5N1 was reported in Buzău, Romania in a wild goose found dead a week ago.

March 6, 2006

- Poland confirms H5N1 in two swans.

March 8, 2006

- Albania has reported its first case of H5N1, found in a domestic chicken in the village of Cukes, near Sarandë, in the south of the country.
- Myanmar found H5N1 in chickens after an HPAI outbreak on March 8.

March 9, 2006

- Serbia (and by extension, Serbia and Montenegro) has confirmed that a wild swan found dead near Sombor carried the deadly H5N1 bird flu, the first confirmed case in the country.

March 10, 2006

- Poland has confirmed that a wild swan found dead near Lublin carried the H5 bird flu, it was the second confirmed case in the country.

March 12, 2006

- Cameroon reports its first outbreak of the H5N1 in a duck farm in Maroua, in the Far North Province.

March 14, 2006

- Azerbaijan reports three deaths from the H5N1 virus.

March 15, 2006

- Sweden has confirmed its first case of H5N1 in two wild ducks found near the Baltic Sea port city of Oskarshamn.
- Culling begins in Jalgaon, Maharastra, India.
- Denmark has confirmed its first case of H5N1 in one Common Buzzard found dead at a beach near the city of Næstved.

March 16, 2006

- Afghanistan finds deadly H5N1 virus.

March 17, 2006

- H5N1 bird-flu strain had been found in tens of thousands of poultry in Israel.

March 18, 2006

- Egypt has confirmed the first human death caused by H5N1 virus.

March 19, 2006

- Egypt has reported its second human case of bird flu, a 30-year-old man who worked on a chicken farm in the province of Qalyoubiya.

March 20, 2006

- Kazakhstan has reported another outbreak of H5N1 in the western part of the country, found in a wild swan.

- Another outbreak of H5N1 in Malaysia resulted in the death of six chickens in the province of Seberang Perai, in the state of Penang.

March 21, 2006

- Pakistan confirms its first cases of H5N1 at chickens in two farms in the Khyber Pakhtunkhwa province.

March 24, 2006

- A dead wild buzzard is found to be the first case of H5N1 in Berlin, Germany.
- H5N1 confirmed in the Gaza Strip, the West Bank and Jordan.

March 26, 2006

- A peregrine falcon in the Tin Shui Wai, which is in Yuen Long of Hong Kong has been confirmed to have died as a result of H5N1 infection.

March 29, 2006

- The Czech Republic confirms its first case of H5N1 in a swan on the Vltava River, near Hluboká nad Vltavou.
- The EU reference laboratory in Weybridge, Great Britain confirms the first case of H5N1 found in Denmark a few weeks before.

March 30, 2006

- A dead swan confirmed to have H5N1 is found in the city of Grudziądz in northern Poland.

March 31, 2006

- First human case of the bird flu was announced in Jordan.

April

April 3, 2006

- The World Health Organization confirmed four cases of bird flu in Egypt over the past month, including two fatalities, the first reports of human deaths due to H5N1 in Africa.

April 4, 2006

- Burkina Faso has detected H5N1 in poultry on the outskirts of the capital, Ouagadougou, making the West African country the fifth nation on the continent

to report the disease. Nigeria, Niger, Cameroon and Egypt have already confirmed the virus in Africa.

April 5, 2006

- H5N1 is detected in domestic poultry near Leipzig, Germany.

April 6, 2006

- H5N1 is detected in a wild migratory swan (Whooper Swan *Cygnus*) in Cellardyke in Fife, Scotland.
- British authorities declare a 1,000 mile (1600 km) wild bird risk area around Cellardyke.

April 10, 2006

- Over one hundred outbreaks have been reported in Myanmar since March 13, the first time since 2004 that H5N1 has been detected in the country.
- A wild swan found in the Sava River, near the Croatian capital of Zagreb, is confirmed to have H5N1.

April 11, 2006

- "The Scientific Seminar on Avian Influenza, the Environment and Migratory Birds met from 10–11 April 2006 at UN Office in Nairobi, Kenya. The Seminar was organized by the United Nations Environment Programme (UNEP) Division of Early Warning and Assessment (DEWA) in cooperation with the Convention on Migratory Species of Wild Animals (CMS) and its Agreement on the Conservation of African-Eurasian Migratory Waterbirds (AEWA). [...] Hepworth identified the Seminar's objectives to: stimulate debate on the role of wild birds in transmitting the virus; provide up-to-date status reports and advice for decision-makers; increase awareness of the recent Multilateral Environmental Agreement (MEA) resolutions among all governments; promote further research on virus behavior and transmission; and encourage international technical cooperation and risk mitigation." The seminar concluded with reaffirmations to disseminate the Seminar's findings and to manage the risks associated with HPAI.

April 12, 2006

- The Panel on Animal Health and Welfare (AHAW) of the European Food Safety Authority (EFSA) publishes a scientific statement on the role of migratory birds in the spread of the H5N1 form of avian influenza (AI) amongst domestic and wild bird populations in the European Union (EU). The statement was supplemented by a formal opinion released on May 12, 2006.

April 18, 2006

- Sudan reports its first case of H5N1 at a poultry farm in Khartoum, as well as the state of Al Jazirah.

May

May 5, 2006

- "Ivory Coast prepared to slaughter chickens and tightened restrictions on movements of poultry on Thursday after reporting outbreaks of bird flu in two heavily populated neighbourhoods of its main city Abidjan. The World Organisation for Animal Health (OIE) said late on Wednesday a total of 17 birds infected with the deadly H5N1 strain of avian influenza had been found in separate outbreaks in the Marcory Anoumabo and Treichville suburbs of Abidjan."

May 11, 2006

- "Djibouti said on Thursday that one person had tested positive for the deadly H5N1 avian influenza virus in the first confirmed human case in the Horn of Africa."

May 13, 2006

- WHO investigated possible H5N1 human cluster in North Sumatra. According to local tests, five members of an extended family have died of bird flu in the past few days.

May 15, 2006

- According to local tests, a sixth member of an extended family have died of bird flu in the past few days in North Sumatra.

May 16, 2006

- According to UN officials, bird flu was found on the western half of the island of New Guinea.

May 21, 2006

- The H5 strain of Bird flu is confirmed in the Romanian capital Bucharest.
- An eighteen year old shuttlecock maker from East Java has died of bird flu. It appears that he was not in direct contact with live birds.

May 24, 2006

- WHO reports cluster of seven victims connected only by each other indicating possible human to human spreading of H5N1

May 25, 2006

- 56 outbreaks of H5N1 have been found in Romania since the virus reemerged there 12 days ago. "The recent outbreaks have involved some large commercial farms and some poultry in Bucharest, the capital, triggering quarantine orders for some neighborhoods this week."

May 30, 2006

- The WHO publishes the *WHO pandemic influenza draft protocol for rapid response and containment*, detailing a proposed method for stopping the spread of a pandemic strain of H5N1 at the source.

June

June 2, 2006

- Indonesian tests say that a girl on the outskirts of Jakarta died of bird flu. Her brother died on May 30 with similar symptoms, but died before he could receive medical treatment, and was buried before testing could be performed.

June 17, 2006

- The EU reference laboratory confirm the presence of the H5N1 viral strain in birds sent from the Kiskunmajsa region of Hungary for analysis.

June 23, 2006

- A family in Indonesia were confirmed to have had human-to-human spread of H5N1. A mutated strain was found, but it had not mutated into an easily-transmissible strain.

June 30, 2006

- "This week's issue of the Weekly Epidemiological Record, published online by WHO, sets out results from the first analysis of epidemiological data on all 205 laboratory-confirmed H5N1 cases officially reported to WHO by onset date from December 2003 to 30 April 2006. Data used in the analysis were collected for surveillance purposes. Quality, reliability and format were not consistent across data from different countries. Despite this limitation, several conclusions could be reached.

1. The number of new countries reporting human cases increased from 4 to 9 after October 2005, following the geographical extension of outbreaks among avian populations.
2. Half of the cases occurred in people under the age of 20 years; 90% of cases occurred in people under the age of 40 years.
3. The overall case-fatality rate was 56%. Case fatality was high in all age groups but was highest in persons aged 10 to 39 years.
4. The case-fatality profile by age group differs from that seen in seasonal influenza, where mortality is highest in the elderly.
5. The overall case-fatality rate was highest in 2004 (73%), followed by 63% to date in 2006, and 43% in 2005.
6. Assessment of mortality rates and the time intervals between symptom onset and hospitalization and between symptom onset and death suggests that the illness pattern has not changed substantially during the three years.
7. Cases have occurred all year round. However, the incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. **If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007."**

July

July 5, 2006

- "Nigeria has been infected multiple times with H5N1 bird flu probably carried by migratory birds from southern Russia and northern Europe or introduced by imported chickens, scientists said on Wednesday. After analysing samples from infected birds on two farms in south-western Nigeria they found the viruses were genetically distinct from each other and from H5N1 found in the north of the country. So rather than one strain spreading through the country, different strains had been introduced on separate occasions, which could make controlling the spread of the virus more difficult. [...] The analysed samples were similar to strains found in southern Russia and northern Europe but not from southeast Asia"

July 7, 2006

- "A Spanish laboratory has confirmed the country's first case of H5N1 bird flu after analyzing a sample taken from a wild migratory water bird" (the *Great Crested Grebe*). Analysis shows that the bird is unlikely to be from Africa.

July 22, 2006

- "China's official Xinhua news agency says a new bird flu outbreak has killed more than 3,000 chickens in the northwest. The Ministry of Agriculture told Xinhua that the July 14 outbreak in Xinjiang region's Aksu city is under control.

No human infections have been reported. Saturday's report says the deadly H5N1 virus killed 3,045 chickens, and nearly 357,000 more were destroyed in an emergency response. Xinhua says the local agriculture department has quarantined the infected area. The government's last reported outbreak was in the northwestern region of Ningxia earlier this month."

July 26, 2006

- The World Health Organization (WHO) confirmed on July 26, 2006 that a 17-year-old boy who died on July 24, 2006 in the Phichit province of northern Thailand had H5N1 avian influenza, marking the country's first case this year. H5N1 was recently detected in 31 dead chickens in Phichit province. Thai health officials have placed several other people from Phichit province under quarantine. "The country's agriculture minister recently announced bans on poultry imports and the transport of birds [and] the Phichit Provincial Livestock Office declared the Bang Mulnarg district an avian flu-infected area, which allows officials to conduct full-scale disease control efforts, including culling, quarantine, screening, and disinfection of affected sites."

July 28, 2006

- Due to H5N1, about 2,500 chickens died on the Dongbang poultry farm in Xaythany district, Laos beginning July 18, 2006. This is the country's first major outbreak since 2004. "The government of Laos has taken immediate action to control the spread of the virus by culling all chickens in the farm, disinfecting the farm and imposed movement restrictions within the five kilometre surveillance zone", said Wantanee Kalpravidh, FAO regional coordinator for Avian Influenza Projects.

August

August 5, 2006

- A German zoo and a Vietnam theme park both report highly pathogenic H5N1 in their birds.

August 10, 2006

- "Experts tracking the dangerous and economically devastating H5N1 virus have been concerned about Indonesia, where inadequate control methods have led to widespread outbreaks across the vast and densely populated archipelago. Indonesia trailed other affected Asian countries in developing human cases, marking its first in July 2005. But since then cases in Indonesia have cropped up at a rate unparalleled elsewhere. And the country's H5N1 death toll recently surpassed that of Vietnam to make Indonesia the country that has lost the most lives to the virus. Indonesia has logged 56 confirmed human cases, 44 of which

have been fatal. Globally 236 cases of H5N1 infection have been confirmed in 10 countries since late 2003 and 138 of those people have died."

August 12, 2006

- "Cambodia has suffered its second outbreak of bird flu this year in the same province where the H5N1 virus killed a boy in April, officials said on Saturday. The virus was confirmed in more than 1,300 ducks that died in Prey Veng province, 70 km (45 miles) southeast of Phnom Penh, but there were no immediate reports of human infections, they said. *Yes, bird flu is back*, senior Agriculture Ministry official Nou Muth said."

August 18, 2006

- On August 18, 2006, the World Health Organization (WHO) changed the H5N1 avian influenza strains recommended for candidate vaccines for the first time since 2004. "Many experts who follow the ongoing analysis of the H5N1 virus sequences are alarmed at how fast the virus is evolving into an increasingly more complex network of clades and subclades, Osterholm said. The evolving nature of the virus complicates vaccine planning. He said if an avian influenza pandemic emerges, a strain-specific vaccine will need to be developed to treat the disease. Recognition of the three new subclades means researchers face increasingly complex options about which path to take to stay ahead of the virus."

August 25, 2006

- CIDRAP reported on August 25, 2006 on a new US government Web site that allows the public to view current information about testing of wild birds for H5N1 avian influenza which is part of a national wild-bird surveillance plan that "includes five strategies for early detection of highly pathogenic avian influenza. Sample numbers from three of these will be available on HEDDS: live wild birds, subsistence hunter-killed birds, and investigations of sick and dead wild birds. The other two strategies involve domestic bird testing and environmental sampling of water and wild-bird droppings. [...] A map on the new USGS site shows that 9,327 birds from Alaska have been tested so far this year, with only a few from most other states. Last year officials tested just 721 birds from Alaska and none from most other states, another map shows. The goal of the surveillance program for 2006 is to collect 75,000 to 100,000 samples from wild birds and 50,000 environmental samples, officials have said."

September

September 7, 2006

- Indonesian officials reported on September 7, 2006 that a 14-year-old Indonesian girl who died in June was infected with bird flu. The case was discovered during

routine surveillance of blood samples from people who had exhibited flu symptoms. In a change of policy, Health Minister Siti Fadillah Supari reported that "we did not send (the samples) to the WHO (World Health Organisation) because our positive results are usually positive results at the WHO." IOL reports that "until now, Indonesia has always sent blood and tissue samples from suspected human bird flu cases to a WHO laboratory in Hong Kong for confirmation", but that "under a new arrangement Jakarta could confirm infections after two local tests showed the person to have contracted H5N1."

September 13, 2006

- Sudan authorities announced that all the samples taken from chickens in southern Sudan in August and sent to the United Kingdom for further tests had proven positive for the deadly H5N1 bird flu virus.

September 25, 2006

- A 21 year old female from East Java Province in Indonesia was hospitalized for symptoms of H5N1 bird flu. She is the sister of an 11 year old male H5N1 victim who died on September 18. The source of her infection is under investigation. It is believed that she and her brother were both exposed to dead poultry in the household.

September 27, 2006

- WHO confirmed a resurgence of highly pathogenic H5N1 killing domestic chickens near Aswan, in Upper Egypt. "Animals within a one-kilometre radius of the site of infection have been culled and removed for sterile burial."

October

October 4, 2006

- Bird flu no threat so far US government inspectors have stepped up their vigilance against Avian flu after recent scares in Pennsylvania and Maryland. The United States Department of Agriculture and United States Department of the Interior confirmed the presence of H5N1 avian influenza subtypes in samples from wild mallard ducks in Pennsylvania, but say testing has ruled out the possibility of this being the highly pathogenic H5N1 strain that has spread through birds in Asia, Europe and Africa. Test results indicate this low pathogenic avian influenza poses no threat to humans. The agencies say the ducks were sampled in Crawford County, Pennsylvania, in August 2006.

October 11, 2006

- An Egyptian woman who was hospitalized on October 4 is confirmed by Egyptian authorities Egypt's first human case of highly pathogenic H5N1 bird flu virus since May, according to WHO advisor Hassan el-Bushra.

October 16, 2006

- 67-year-old Indonesian woman died of bird flu after being treated at a hospital for more than a week, marking the country's 54th death from the virus, an official at the health ministry said.

October 31, 2006

- A 39-year-old Egyptian woman died of bird flu a month after symptoms first appeared. This was the first case in Egypt since May, 2006.

November

November 2, 2006

- In Thailand, a dog succumbs to bird flu, raising the possibility that pets can contract the disease and potentially spread it to their human owners.

November 13, 2006

- In Indonesia two more cases of H5N1 have been confirmed by the Ministry of Health. One is a 35-year-old female, who developed symptoms on November 7. The second is a 30-month-old male, who developed symptoms on November 5.

December

December 12, 2006

- South Korea announced its third major outbreak of deadly H5N1 in less than three weeks (all three in North Cholla province, 170 km (100 miles) south of Seoul). Over a million birds are being killed to try to contain it. In 2003 - 2004 the country destroyed 5.3 million birds to contain H5N1.

December 18, 2006

- The United States summarized progress the U.S. government has made preparing against an influenza pandemic:

- Federal Pandemic Preparedness Plans: All Federal Departments and Agencies are developing their own pandemic preparedness plans to ensure that they are addressing all elements of a comprehensive checklist.
- Statewide Pandemic Planning Summits: Secretary Leavitt and other senior officials from the Department of Health and Human Services have led Statewide pandemic planning summits in all States. We are investing \$600 million in State and local preparedness efforts, including the exercising of pandemic plans across communities and at all levels of government.
- Community-Wide Mitigation Strategies: We have focused unprecedented attention on the role of community-wide mitigation strategies, such as early school closure, cancellation of public gatherings, and other "social distancing" behaviors in reducing illness during a pandemic. Interim guidance on the ways communities can use these interventions most effectively will be released in January.
- Vaccine Production: We have invested over \$1 billion in the development of new cell-culture technologies for influenza vaccine production, and will soon announce contracts to adapt existing egg-based vaccine facilities for pandemic vaccine production.
- Adjuvants: Very promising results on the testing of "dose-stretching" materials, also known as "adjuvants", have recently been announced by companies involved in this research. If proved to be safe and effective, adjuvants could allow a dramatic reduction in the amount of vaccine necessary to immunize a person against a pandemic virus, thereby allowing us to vaccinate many more people with our vaccine stockpile.
- Rapid Diagnostic Tests: We have invested in the development of rapid diagnostic tests, to allow swift recognition of a pandemic virus in the human population, thereby allowing rapid isolation and treatment of infected individuals.
- Bird Surveillance System: We have put a nationwide wild bird surveillance system in place to provide early warning of an outbreak of H5N1 in the bird population, and are reporting the results of these efforts to the public on an ongoing basis.
- International Efforts: We have invested \$434 million in international efforts, far more than any other nation, in an effort to build infrastructure in affected regions of the world to rapidly recognize and respond to an outbreak of a pandemic virus. In addition to improving these nations' ability to control outbreaks of H5N1 in their bird populations, these systems may make it possible to slow, stop, or limit the spread of a pandemic virus to the U.S.

December 19, 2006

- Vietnam had its first major outbreak of deadly H5N1 in thirteen months on December 6, 2006 due to chickens not being vaccinated because they had been hatched illegally. "There is a real threat now of the disease spreading to other places since the farmers threw away the birds' carcasses before the outbreak came to light."

December 24, 2006

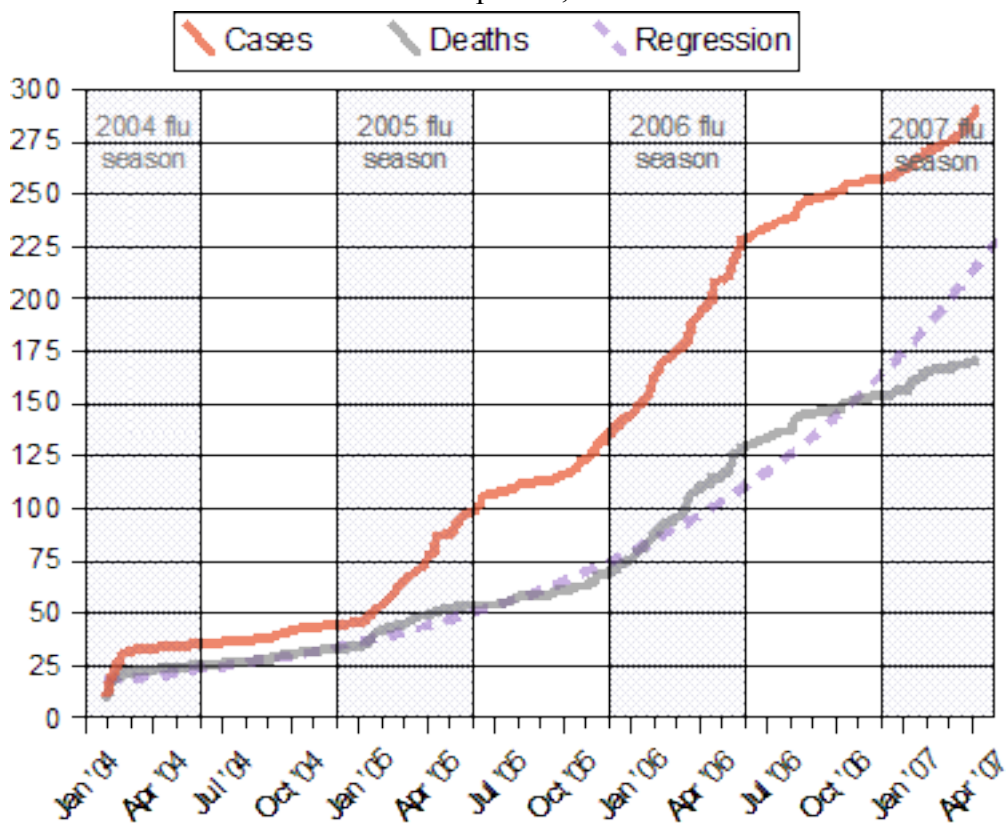
- In Egypt a woman died of H5N1, hours after tests confirmed she and two other members of her extended family had been suffering from the highly pathogenic virus. The 30-year-old woman had been in the hospital since December 17, 2006, but doctors had not immediately suspected bird flu as she denied having had contact with poultry. The woman was part of an extended family of 33 living in a single house in a village near the town of Zifta in Gharbiya province, about 80 km north of Cairo, and was the third family member diagnosed with bird flu in 24 hours. Earlier, the World Health Organisation confirmed two siblings from the same house, a brother, 26, and sister, 15, had the virus. The family raised ducks in their home, and the brother and sister had slaughtered the flock after a number of ducks had become sick and died.

Chapter 14

Global Spread of H5N1 in 2007

Cumulative Human Cases of and Deaths from H5N1

As of April 11, 2007



Notes:

- Source WHO Confirmed Human Cases of H5N1
- "[T]he incidence of human cases peaked, in each of the three years in which cases have occurred, during the period roughly corresponding to winter and spring in the northern hemisphere. If this pattern continues, an upsurge in cases could be anticipated starting in late 2006 or early 2007."
Avian influenza – epidemiology of human H5N1 cases reported to WHO
- The regression curve for deaths is $y = a + e^{kx}$, and is shown extended through the end of April, 2007.

The **global spread of (highly pathogenic) H5N1** in birds is considered a significant pandemic threat.

While prior H5N1 strains have been known, they were significantly different from the current H5N1 strain on a genetic level, making the global spread of this new strain unprecedented. The current H5N1 strain is a fast-mutating, highly pathogenic avian influenza virus (HPAI) found in multiple bird species. It is both epizootic (an epidemic in non-humans) and panzootic (a disease affecting animals of many species especially over a wide area).

In January, Japan, Hungary, Russia, and the United Kingdom joined the list of nations seeing a resurgence of bird deaths due to H5N1. In February, Pakistan, Turkey, Afghanistan, and Myanmar joined the list and Kuwait saw its first major outbreak of H5N1 avian influenza.

In March Bangladesh and Saudi Arabia each saw their first major outbreak of H5N1 avian influenza and Ghana in May.

As H5N1 continued killing many birds and a few people throughout the spring in countries where it is now endemic, in June Malaysia and Germany saw a resurgence of bird deaths due to H5N1, while the Czech Republic and Togo experienced their first major outbreak of H5N1 avian influenza.

In July France and India also saw a resurgence of bird deaths due to H5N1.

January

- January 11, 2007: "South Korean officials say the bird flu virus had been transmitted to a human during a recent outbreak among poultry, but the person showed no symptoms of disease."
- January 11, 2007: "Bird flu reaches another province in southern Vietnam, spreading to flocks in two new areas in as many days. Some 20 unvaccinated chicks died suddenly over the weekend at a farm in Vinh Long province, and test results came back positive for the lethal H5N1 strain."
- January 12, 2007: "In Nigeria, a new outbreak of the H5N1 virus is reported in birds in Sokoto and Katsina states."
- January 14, 2007: "Japanese agricultural officials confirmed yesterday that the virulent H5N1 bird flu virus caused the deaths of thousands of chickens at a poultry farm in southern Japan this week [...] Japan's most recent [prior] outbreak occurred in Kyoto in 2004."
- January 16, 2007: "A new outbreak of virulent bird flu is confirmed in ducks in northern Thailand -- the first such case in six months. About 100 ducks were

reported dead and tested in Phitsanulok province. Wild and free-range ducks within a 3-miles radius are being culled as a precaution."

- January 17, 2007: Indonesia Works to Stem Bird Flu Cases - Indonesia plans to slaughter hundreds of thousands of backyard chickens over the next few weeks in a bid to stem a surge in human deaths from the H5N1 virus. Indonesia has recorded 61 deaths from bird flu, including four in the last week.
- January 18, 2007: "Mutations in the bird flu virus have been found in two infected people in Egypt, in a form that might be resistant to the medication most commonly used to treat the deadly disease, the WHO said. The mutations in the H5N1 virus strain were not drastic enough to make the virus infectious enough to spark a pandemic, but officials said more such mutations could prompt scientists to rethink current treatment strategies."
- January 20, 2007: "South Korea prepares to slaughter 273,000 poultry after an H5N1 outbreak at a chicken farm."
- January 25, 2007: "The European Commission has confirmed the presence of H5N1 in a farm in the southeastern Hungary."
- January 29, 2007: There was an outbreak of H5N1 at three farms or households in the Krasnodar territory, an agricultural region in the southern part of European Russia on the Black Sea, Russian officials said on January 29, 2007.

February

- February 3, 2007: In late January 2007 there was an outbreak of avian influenza, caused by H5N1, at one of Bernard Matthews' farms in Holton in Suffolk. This infection, the second in the United Kingdom, was confirmed on 3 February 2007. A 3 km protection zone, 10 km surveillance zone and a restricted zone encompassing 2000 km² were set up and 159,000 turkeys were slaughtered with the cull being completed on 5 February. Around 320 workers at the plant were given anti-viral drugs. The plant was thoroughly disinfected. with cleaning complete on February 12 and permission being given for production to resume. Neither causation, nor a link with the Bernard Matthews plant in Hungary, has been established but the H5N1 bird flu strains found in geese in Hungary and the turkeys in Britain are 99.96% genetically identical, and almost certainly linked, according to an analysis of the viruses by the Veterinary Laboratories Agency in Weybridge, Surrey.
- February 6, 2007: H5N1 was found in a flock of 40 chickens near Islamabad, Pakistan and all the chickens are now dead from the disease bird flu or culling to prevent its spread.

- February 9, 2007: H5N1 killed 170 chickens in Bogazkoy village, in southeastern Turkey. Nearly 1,000 birds have been culled in Bogazkoy and two nearby villages."
- February 19–20, 2007: "An outbreak of H5N1 detected at two farms near the Laotian capital Vientiane on Feb. 7 was reported."
- February 22, 2007: "H5N1 is been confirmed in eight suburban Moscow districts, a top Russian veterinary official said, as experts enforced a quarantine in several villages and sought to keep the disease from spreading. The virus, which began killing domestic birds in the Moscow suburbs on Feb. 9, has been traced to a single animal market just outside the capital."
- February 22, 2007:"Afghan authorities were culling poultry after an outbreak of the deadly H5N1 strain of bird flu in chicken in an eastern Afghan city, a U.N. official said Wednesday."
- February 25, 2007:Kuwait saw its first major outbreak of H5N1 avian influenza.
- February 28, 2007:"Myanmar reported that the H5N1 virus killed poultry at a farm about 5 miles from Rangoon, the country's largest city [...] The outbreak began 2 days ago, killing 68 of 1,360 layer chickens, ducks, and pullets, and officials attributed the outbreak to poor biosecurity on the farm, the report said. The remaining birds were destroyed, and authorities instituted several control measures including limiting poultry movement within the country, screening poultry, and disinfecting the affected area. Myanmar's last poultry outbreak was reported in April 2006."

March

- March 5–6, 2007: "China reports bird flu struck a poultry market in the Tibetan capital of Lhasa, prompting the culling of nearly 7,000 birds. The outbreak began March 1."
- March 22, 2007: Bangladesh saw its first major outbreak of H5N1 avian influenza. "The virus was found in the birds from a poultry firm run by Bangladesh's National Airlines Biman, which has already culled 30,000 birds over the last few days."
- March 23, 2007: "Saudi Arabia's agriculture ministry has said the deadly H5N1 strain of bird flu had been discovered in [...] peacocks, turkeys, ostriches and parrots [and all] birds in the area had been culled. [...] The last reported cases of bird flu in Saudi Arabia involved 37 falcons in 2006. Last month, Saudi Arabia lifted bans going back to 2004 on poultry imports from 42 countries."

April

- April 6, 2007: "A 13-year-old Cambodian girl dies from bird flu, bringing the country's death toll from the H5N1 virus to seven."

May

- May 3, 2007:"Ghana's first case of the highly pathogenic H5N1 bird flu has been confirmed in sick chickens by local laboratories and a US naval laboratory in Egypt, a World Health Organisation official said overnight. Some 1600 birds had already been incinerated as part of efforts to control the outbreak on a farm 20km east of Ghana's capital Accra, near the port of Tema".

June

- June 5, 2007:" As Bangladesh battles to root out the lethal strain of bird flu known as H5N1 that has spread among its poultry flocks, the ability of the virus to thrive could be aided by the millions of ducks in that country."
- June 6, 2007: Malaysia joined the list of nations seeing a resurgence of bird deaths due to H5N1.
- June 12, 2007: "Indonesia finds traces of H5N1 in apparently healthy-looking poultry, making it tougher to detect the disease in the country hardest hit by the virus, officials said. Sick or dead chickens are used as a sign of H5N1 infection, but the appearance of "asymptomatic" chickens means humans could become more easily infected with bird flu."
- June 21, 2007: The Czech Republic saw its first major outbreak of H5N1 avian influenza.
- June 23, 2007: Togo saw its first major outbreak of H5N1 avian influenza. In Germany seven dead wild birds (five swans, one duck, one goose) tested positive for H5N1, the first such cases reported in Germany this year.

July

- July 6, 2007: "German authorities discover H5N1 in domestic poultry for the first time this year. Officials say a goose in the town of Wickersdorf in the state of Thuringia was found to be infected."
- July 5, 2007:In July France joined the list of nations seeing a resurgence of bird deaths due to H5N1. Three dead swans in France were found to have the deadly form of H5N1.

- July 26, 2007: In July India joined the list of nations seeing a resurgence of bird deaths due to H5N1. The outbreak was reported in Manipur which borders the country of Myanmar. 132 chickens out of 144 died over a period of six days starting July 7. Over 150,000 birds within a five-km radius of the infected farm "will be culled in the next 10 days."

August

- August 22, 2007: On August 22, 2007, an Indonesian woman, 28, chicken trader, was the 2nd person to die of bird flu in Bali, raising the death toll in the nation due to the disease to 84 (after 4 days of hospitalization). Tests in 2 local laboratories was positive for the H5N1 strain of the disease. 194 people — the majority of them in Indonesia died since 2003, according to the World Health Organization.

September

- September 17, 2007: "In its first H5N1 bird flu outbreak since May, China's Ministry of Agriculture confirmed on its Web site that 36,130 ducks had been culled following the outbreak in Panyu district of the southern metropolis of Guangzhou, not far from Hong Kong."

October

- October 8, 2007: "An Indonesian Health Ministry official says a 44-year-old woman has died from bird flu after buying chickens at a local market, lifting the national death toll from the disease to 87."
- October 25, 2007: "Vietnam reports its third outbreak among poultry this month, this time in the village of Lung Na near the Chinese border. The virus has already struck duck farms in the central province of Quang Tri and Tra Vinh."

November

- November 12, 2007: "An outbreak of bird flu in eastern England is the deadly H5N1 strain of the disease. The source of the outbreak had not yet been identified, acting chief veterinarian official Fred Landeg said. Officials said earlier that about 5,000 free-range turkeys, 1,000 ducks and 500 geese on the affected farm would be killed."
- November 29, 2007: "Authorities continue to conduct tests for bird flu in Romania's eastern Danube Delta, a day after they confirmed an outbreak of the virus in hens and ducks on a small farm in the village of Murighiol, a delta village 155 miles northeast of the capital, Bucharest."

December

- December 1, 2007: "Three poultry farms northwest of Warsaw, Poland were cordoned off after the deadly H5N1 strain of bird flu was found in turkeys, officials said on Saturday. The cases were found at farms around the village of Brudzen near the city of Plock. Officials say the virus was most likely brought to Poland by migrating ducks, geese or swans."
- December 10, 2007: "Chinese health authorities said they were hunting for the causal link between a son and his father both struck by bird flu, but have found no evidence that the virus has mutated into a new strain. The 52-year old father was diagnosed with the H5N1 strain of bird flu late last week in the eastern province of Jiangsu, days after his 24-year old son died from the disease."