A new H1N1 triple-reassortant “swine” influenza virus was recently described in individuals from the United States and Mexico who presented with respiratory symptoms, and the same virus was subsequently confirmed in patients from several countries around the world. The circumstances surrounding the emergence of this pathogen, and the factors that facilitated the initial cross-species transmission, are still incompletely understood. It became apparent in the early days of the outbreak that the virus can be directly transmitted between humans. Pathogens that originate in animal reservoirs and subsequently acquire the potential for human-to-human transmission have caused outbreaks throughout human history. Although each outbreak is marked by its own particularities, it is important to remember the teachings that emerge from previous epidemics and pandemics. Integrating the important lessons of the past will provide the best opportunity to understand host-pathogen interaction and the most powerful approach to implementing effective prophylactic and therapeutic measures.

On 17 April 2009, the Centers for Disease Control and Prevention reported that a girl, age 9 years, and a boy, age 10 years, who had flu-like symptoms and lived in adjacent counties in California, had tested positive for an H1N1 “swine” influenza virus (1). Mexico City had reported influenza-like illnesses on 18 March. By 13 May 2009, the strain—which seems to be a reassortant virus (Figure 1) with nucleotide sequences derived from swine, avian, and human viruses (2)—was confirmed in patients from Mexico, the United States, Canada, Spain, the United Kingdom, and at least 28 other countries. The virus derives the name “swine” from the animal reservoir thought to be responsible for initiating the outbreak in humans. An animal source was not required for subsequent infection because direct human-to-human transmission had become possible.

An estimated 58% of the 1407 known human pathogens are zoonotic, which means that they normally occur in animals but also infect humans (3). After a microorganism crosses the species barrier, a major concern is whether it can be directly transmitted between humans, who tend to be in closer contact with other humans than with animal reservoirs. Microorganisms that gain this ability have historically caused the most devastation. The notorious 1918 influenza pandemic—deservedly known as the “mother of all pandemics”—infected more than one quarter of the world’s population and claimed an estimated 50 to 100 million human lives (4). Its origins have always been debated. Some have proposed that the virus resided in an avian reservoir and entered the human population either directly from birds or indirectly through an intermediate host, facilitated by overcrowding and by the proximity of pigs, chickens, ducks, and geese (5). The reconstructed 1918 influenza virus can replicate and cause respiratory disease in swine, and scientists believe that it continued to circulate in swine after its introduction into the pig population during the pandemic (6). Whereas human influenza viruses do not easily infect birds and avian viruses do not replicate efficiently in humans, swine have repeatedly been shown to serve as “mixing vessels” that allow genetic reassortment between different influenza virus strains (5, 7).

Two features of the influenza virus, compounded by current globalization trends, explain its ability to become a particularly worrisome zoonotic threat. One feature is the high error rate during genomic replication, which is typical of RNA viruses. The other is the segmented influenza virus genome, which facilitates reassortment between different viral strains that infect the same cell (Figure). At a time when air travel makes it possible to reach the most remote corners of the planet in a matter of hours, any emerging or reemerging infectious disease stops being a local issue and instead becomes a global medical and public health priority. These considerations explain why, for a long time, the question about the next influenza pandemic has not if, but when (8).

Details of how the current influenza virus emerged, although still scarce, will enhance our knowledge about factors that enable viruses to cross the species barrier and cause disease in humans. The importance of human–animal contact in occupational settings will probably be a key take-home lesson. Farmers, meat-processing workers, and veterinarians have had markedly higher antibody levels against swine influenza viruses—sometimes concomitantly against 2 isolates—than control participants (7), and a pregnant woman who visited a Wisconsin country fair that displayed pigs developed a fatal infection in 1998 (9). This echoes a lesson from the severe acute respiratory syndrome (SARS) outbreak: In the winter of 2003 to 2004, after the World Health Organization declared an end to the SARS epidemic, 4 new cases were reported in Guangdong Province, China. Epidemiologic investigation revealed that 2

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The influenza virus single-stranded RNA genome is organized into 8 segments. In a process known as reassortment, 2 or more viruses that co-infect the same cell can exchange 1 or more RNA segments to generate strains with new antigenic properties and new biological characteristics. During the 1957 "Asian influenza" pandemic, 3 genes from an avian H2N2 virus were introduced into a human H1N1 strain and created a new virus with pandemic capabilities. This exchange of genetic material probably occurred during the dual infection of a human or an animal, possibly a pig, with both viral strains. Derived from reference 25.

of the patients were a 20-year-old waitress who worked in proximity to civet cages and a 40-year-old physician whose dining table in the same restaurant was within 5 meters of the cages (10). All palm civets from the restaurant tested positive for the SARS coronavirus, and sequencing of the S gene that encoded its attachment protein implicated this virus, rather than the one circulating from the previous epidemic, as the source of the outbreak.

After a pathogen crosses a species barrier, epidemic spread requires efficient direct transmission within the population. Although several studies have focused on the mechanistic details of airborne virus dissemination, our understanding of human-to-human influenza transmission is, as recently characterized, "woefully inadequate" (11). Air travel clearly plays an important role in establishing infectious foci in new countries. Although human-to-human transmission during air travel has been thought to require flights as long as 8 hours and to affect only passengers seated within 2 rows of the index patient (12), this view is changing because of reports of in-flight spread occurring over considerable distances within the cabin and during shorter flights. In 1977, 72% of the passengers on an Alaska Airlines flight, which was delayed for 3 hours while the aircraft sat on the tarmac, developed influenza within 72 hours (13). On a 3-hour flight between Hong Kong and Beijing on 15 March 2003, passengers sitting as far as 7 rows from an index patient developed SARS (14). Epidemiologic details from the current H1N1 outbreak should significantly complement our understanding of in-flight airborne pathogen transmission, an important facet of global preparedness planning.

With ever-expanding air traffic volumes, the global spread of pathogens is changing. When researchers modeled the 1968 to 1969 Hong Kong influenza pandemic (15) on the basis of data regarding air travel in 53 cities in the year 2000, they found that the virus spread almost simultaneously in the Northern and Southern hemispheres—which underscores the narrowness of the period during which intervention could halt the epidemic. Of note, the study also predicted that Sydney and Johannesburg, which were the 48th and 45th cities, respectively, to be affected in 1968, would be among the first cities to report cases in 2000. New Zealand was one of the first countries outside Mexico to report patients in the current H1N1 outbreak, which confirmed the prediction of very rapid spread to distant countries.

Strong international collaborative efforts, such as those that occurred during the SARS outbreak, can have a dramatic effect on an epidemic. The delayed reporting from China, where the first case of SARS was diagnosed on 16 November 2002 but not investigated by World Health Organization officials until 12 April 2003, contrasts with the quick communication from Vietnam about the index cases (16, 17). This prompt response is credited with effectively controlling the outbreak in Vietnam and making it the first country to be declared SARS-free and removed, on 28 April 2003, from the World Health Organization list of travel advisories (18). During the current pandemic, the proactive reporting of new infections and the decision by Mexican officials to close schools and businesses in the wake of the outbreak, along with the prompt implementation of screening checkpoints and quarantines in many countries, may have substantially slowed the global spread of the infection.

Social isolation measures save lives. In the fall of 1918, Philadelphia, Pennsylvania, had much higher flu mortality rates than did St. Louis, Missouri. In Philadelphia, city officials allowed a 28 September citywide parade to continue despite having identified the first cases on 17 September. They banned public gatherings and closed schools only on 3 October. In comparison, St. Louis, where the first cases occurred on 5 October, adopted social distancing measures on 7 October. As a result, the peak weekly excess pneumonia and influenza death rate between 8 September and 28 December was 8.3 times higher in Philadelphia than in St. Louis (19). A survey that examined the responses of 17 U.S. cities during the 1918 pandemic con-

Figure. Reassortment of influenza virus.

The influenza virus single-stranded RNA genome is organized into 8 segments. In a process known as reassortment, 2 or more viruses that co-infect the same cell can exchange 1 or more RNA segments to generate strains with new antigenic properties and new biological characteristics. During the 1957 “Asian influenza” pandemic, 3 genes from an avian H2N2 virus were introduced into a human H1N1 strain and created a new virus with pandemic capabilities. This exchange of genetic material probably occurred during the dual infection of a human or an animal, possibly a pig, with both viral strains. Derived from reference 25.
cluded that early implementation of nonpharmacological interventions, including social isolation measures, lowered excess mortality rates by 50% (19).

Although initial studies in infectious disease epidemiology assumed that individuals within a population transmit the microorganism at similar rates, transmission from individuals known as super-spreaders is much more efficient. In what is known as the 20/80 rule, 20% of infectious persons are thought to contribute at least 80% of the net transmission potential of a microorganism (20). During the SARS outbreak, a 44-year-old man in China infected 35 cases by direct contact (21). In the Hong Kong SARS outbreak, a super-spreader had a runny nose, an uncommon manifestation in SARS, in addition to the cough, fever, and malaise present in other patients. Some investigators have proposed that co-infection with other viruses might make a patient particularly infectious (22, 23). Investigative efforts during the current and future outbreaks should therefore focus on identifying patients who exhibit atypical or uncommon manifestations of influenza.

Insight into the influenza virus genome has provided valuable information with potential medical and public health benefits. Unlike the 1957 and 1968 pandemics, which were caused by reassortment between avian and human strains, the pandemic in 1918 was most likely caused by an avian virus that accumulated mutations and, subsequently, evolved and adapted to humans (24). Thus, at least 2 mechanisms could explain zoonotic outbreaks (25). In addition, analysis of amino acid substitution rates in the 1918 virus suggest that genes of avian origin could have been circulating in human influenza viruses as early as 1900, which points toward the possibility of detecting sequence modifications years before zoonotic pathogens cause human epidemics (24, 25). The sequence of the current H1N1 strain will probably provide clues about how this virus emerged and what factors enabled animal-to-human and then human-to-human transmission. We must learn, from all the zoonotic pathogens that have afflicted humankind, the particular circumstances that facilitated each outbreak. If we can integrate this information successfully, we will understand what makes us vulnerable to pathogens that cross species barriers.

As an important lesson with immediate applicability, it is essential to appreciate the value of nonpharmacologic interventions during outbreaks. We can save many lives if we maintain a high index of clinical suspicion in persons with occupational or casual exposure to animals that present zoonotic potential and quickly implement social distancing measures. These 2 actions are highly beneficial, particularly during the initial stages of an outbreak, when limited information is available on the biology of the pathogen. It is then that an alert clinician can make a big difference.

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