On 31 March 2013, Chinese public health authorities notified the World Health Organization of the isolation of influenza A(H7N9) virus from 3 critically ill adults (1). This avian influenza virus had never before been detected in humans, and its association with severe disease electrified influenza experts. Could this foreshadow a pandemic? The cases generated many questions for public health authorities, influenza scientists, clinicians, and the public. Many remain to be answered, but the answers to 2 seem clear.

**Should We Be Concerned?**

To cause a pandemic, an influenza virus should fulfill 3 conditions. First, a substantial portion of the population should not be immune. Because H7N9 viruses have never circulated among humans, population immunity is unlikely.

Second, the virus should be capable of causing disease. Through the efforts of the Chinese public health community to rapidly share information, we have an early view of the emergence of H7N9. The number of sporadic cases has increased rapidly. As of 23 April 2013, less than 2 months after the first reports, 108 laboratory-confirmed cases have been reported from China and 22 people have died. Almost all patients have been hospitalized, and most have severe disease. The severity and mortality rate are probably inflated to some degree by detection of such cases (the “tip of the iceberg”) and perhaps late initiation of antiviral therapy. Indeed, the apparent case-fatality rate has fallen in recent weeks. Determining the true severity is critical and requires widespread viral testing, collection of clinical data, and serologic studies.

The rapid sharing of genetic sequence information has provided insight into this virus. Our understanding of the molecular characteristics that translate into species specificity, virulence, and ease of spread is evolving. The virus has several disturbing features. The genetic sequence of viruses from 3 patients as well as H7N7 viruses from live-bird markets shows adaptation to mammalian hosts (2, 3). Mutations are present in the receptor binding site of the hemagglutinin protein that are associated with increased binding to human-type α2–6-linked sialic acid receptors, as is a mutation in the polymerase basic 2 protein associated with efficient replication in mammals. A deletion in the neuraminidase protein is present that has been associated with adaptation to terrestrial birds and increased virulence in humans. Like those viruses, and in contrast to influenza A(H1N1)pdm09 virus, the isolates of H7N9 viruses express a full-length PB1-F2 protein. This recently discovered protein is associated with pathogenicity in the highly lethal 1918 H1N1 virus and the H5N1 virus. Together, these features suggest the existence of a virus adapted to infecting humans and capable of causing severe disease.

The third and most critical characteristic of pandemic strains is efficient human-to-human transmission. Despite extensive investigation and testing of contacts, only a few instances of probable transmission have been identified. We still cannot identify genetic features that would tell us if H7N9 had the ability to mutate and spread efficiently, one of the goals of the controversial “gain-of-function” experiments (4), in which researchers created strains of influenza A(H5N1) that were transmissible among ferrets (5, 6). Thus, H7N9, like H5N1, is hard to catch but dangerous for those who become infected. Detection of more than 100 cases in 2 months compared with roughly 600 human cases of H5N1 infection in a decade suggests that H7N9 is already more transmissible than H5N1, at least from poultry to humans.

**Are We Fully Prepared for a Pandemic?**

Despite substantial progress over the past decade, we continue to have vulnerabilities. In 2012, the Infectious Diseases Society of America highlighted and assessed 10 principles focusing on how to prepare and respond to seasonal and pandemic influenza and addressed the gaps (7). In several of these, investments have improved preparedness. Experimental seed strains for vaccines are being produced and evaluated using new techniques. Cell culture–based and recombinant protein expression system–based vaccines are now licensed in the United States. These advances may allow for more rapid production of vaccine. However, past H7 strains have been poorly immunogenic (8), and use of adjuvants may be necessary.

Molecular diagnostic assays for influenza are more widely available than in 2009, and H7N7-specific assays could be rapidly deployed. However, rapid and accurate point-of-care assays are still needed. The need for coordinated surveillance and improved international collaboration was highlighted. To date, the response of the Chinese authorities has been remarkable. Nonetheless, we should not underestimate the difficulty in communicating complex and rapidly changing information among stakeholders, including the public.

In some critical areas, we remain at risk. Antiviral agents are potentially life-saving tools. Many developed countries have substantial stockpiles of oseltamivir. Most isolates tested to date have been reported to be sensitive to both oseltamivir and zanamivir, but 1 isolate, A/Shanghai/1/2013, contains the R294K mutation in neuraminidase...
that can confer oseltamivir resistance (9). Emergence of resistance to oseltamivir would greatly limit treatment options, especially for more severely ill patients. Zanamivir is likely to remain an active option, but supplies are limited and the inhaled powder formulation restricts use in some populations. Intravenous preparations of zanamivir and peramivir are in advanced development, and a sialidase fusion construct (DAS181) is in phase 2 study, but this is a slim pipeline (10). We need to develop more treatment options, including agents that could modify the inflammatory cascade and treat secondary infections.

Finally, the Infectious Diseases Society of America’s report (7) emphasized the need for robust public health and clinical infrastructures and a stable funding source for influenza research, preparedness, and response. The deterioration of the public health workforce and limited surge capacity of our stressed health care system would prove dangerous in a pandemic.

It remains uncertain whether influenza A(H7N9) will remain a sporadic zoonosis restricted to East Asia, become a global pandemic, or become something in between. We must maintain a high level of alert and preparedness. We should redouble efforts to fill gaps in our knowledge and toolbox for response and treatment. If, as we hope, this is not the beginning of a pandemic, these efforts will still reduce the annual toll of influenza cases and help prepare for the inevitable but unpredictable appearance of the next pandemic.

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