Global Concerns Regarding Novel Influenza A (H7N9) Virus Infections

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Severe disease in humans caused by a novel influenza A virus that is distinct from circulating human influenza A viruses is a seminal event. It might herald sporadic human infections from an animal source — e.g., highly pathogenic avian influenza (HPAI) A (H5N1) virus; or it might signal the start of an influenza pandemic — e.g., influenza A(H1N1)pdm09 virus. Therefore, the discovery of novel influenza A (H7N9) virus infections in three critically ill patients reported in the *Journal* by Gao and colleagues (pages 1888–1897) is of major public health significance. Chinese scientists are to be congratulated for the apparent speed with which the H7N9 virus was identified, and whole viral genome sequences were made publicly available in relatively short order. Because this H7N9 virus has not been detected in humans or animals previously, the situation raises many urgent questions and global public health concerns.

The key question for pandemic risk assessment is whether there is evidence of either limited or, more important, sustained human-to-human transmission — the latter being indicative of an emerging pandemic. If human-to-human transmission occurs, transmission dynamics, modes of transmission, basic reproductive number, and incubation period must all be determined. It is possible that these severely ill patients represent the tip of the iceberg and that there are many more as-yet-undetected mild and asymptomatic infections. Determining the spectrum of illness will help us understand the scope of the problem and assess severity. Enhanced surveillance for H7N9 virus infection is therefore urgently needed among hospitalized patients and outpatients of all ages with less severe respiratory illness. Other useful information can be derived from monitoring close contacts of patients with confirmed H7N9 cases to assess whether family members or health care personnel who provided care for patients with H7N9 virus infection have respiratory illness and laboratory-confirmed H7N9 virus infection. Such investigations will clarify whether H7N9 virus transmission in people appears efficient, or whether limited, nonsustained human-to-human transmission is occurring in persons with prolonged unprotected exposures, such as in clusters of HPAI H5N1 cases in blood-related family members. So far, the information provided by Chinese health officials provides reassurance that sustained human-to-human transmission is not occurring.

In addition to causing severe illness and deaths, the novel H7N9 viruses reported by Gao and colleagues have genetic characteristics that are of concern for public health. The hemagglutinin (HA) sequence data suggest that these H7N9 viruses are a low-pathogenic avian influenza A virus and that infection of wild birds and domestic poultry would therefore result in asymptomatic or mild avian disease, potentially leading to a "silent" widespread epizootic in China and neighboring countries. If H7N9 virus infection is primarily zoonotic, as reports currently suggest, transmission is expected to occur through exposure to clinically normal but infected poultry, in contrast to HPAI H5N1 virus infection, which typically causes rapid death in infected chickens.

The gene sequences also indicate that these viruses may be better adapted than other avian influenza viruses to infecting mammals. For example, the presence of Q226L in the HA protein has been associated with reduced binding to avian-like receptors bearing sialic acids linked to galactose by α-2,3 linkages found in the human lower respiratory tract,[1] and potentially an enhanced ability to bind to mammalian-like receptors bearing sialic acids linked to galactose by α-2,6 linkages located in the human upper airway.[1] Equally troubling is that Q226L in HA has been shown to be associated with transmission of HPAI H5N1 viruses by respiratory droplets in ferrets, one of the animal models for assessing pathogenicity and transmissibility of influenza viruses.[2,3] These H7N9 viruses also possess the E627K substitution in the PB2 protein, which has also been associated with mammalian adaptation and respiratory-droplet transmission of HPAI H5N1 virus in ferrets.[3] This H7N9 virus is a novel reassortant with HA and neuraminidase (NA) genes from an ancestral avian H7N9 virus and the six other genes from

an avian H9N2 virus. The animal reservoir now appears to be birds, but many experts are asking whether these viruses might also be able to infect pigs, another common reservoir for zoonotic infections. The viral sequence data indicate antiviral resistance to the adamantanes and susceptibility to neuraminidase inhibitors, except for an R292K mutation in the NA protein of the A/Shanghai/1/2013 virus. Because this mutation has been associated with in vitro resistance to neuraminidase inhibitors in another N9 NA subtype virus, additional analyses must be undertaken to understand its significance. It is not known whether this mutation arose de novo in the host or is associated with oseltamivir treatment. Ongoing surveillance is crucial to assessing the emergence and prevalence of H7N9 viruses resistant to available antivirals.

Since available diagnostic assays used in clinical care (e.g., rapid influenza diagnostic tests) may lack sensitivity to identify H7N9 virus and since existing molecular assays will identify H7N9 virus as a nonsubtypeable influenza A virus, a critical public health issue is the rapid development, validation, and deployment of molecular diagnostic assays that can specifically detect H7N9 viral RNA. Such assays have been developed in China and are in development in many countries including the United States, and they will be deployed as they were for the 2009 H1N1 pandemic.[4] Having available H7-specific assays will facilitate surveillance of H7N9 virus infections and help address key questions such as the duration of viral shedding, the infectious period, the optimal clinical specimens for laboratory confirmation, and the spectrum of clinical illness.

The clinical features described in the three patients with H7N9 virus infection, including fulminant pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, multiorgan failure, rhabdomyolysis, and encephalopathy, are very troubling. Clinical care of severely ill patients should be focused on evidence-based supportive management of complications such as ARDS. Adherence to recommended infection-control measures in clinical settings to reduce the risk of nosocomial transmission cannot be overemphasized.

All three patients with H7N9 virus infection reported by Gao and colleagues received late treatment with oseltamivir starting on day 7 or 8 of illness while critically ill. Data related to human infections with seasonal, pandemic, and HPAI H5N1 viruses indicate that the earlier antiviral treatment is initiated, the greater the clinical benefit. Therefore, oral oseltamivir or inhaled zanamivir should be administered to patients with suspected or confirmed H7N9 virus infection as soon as possible. Secondary invasive bacterial infections associated with influenza can cause severe and fatal complications, and appropriate empirical antibiotic treatment for community-acquired bacterial infections may be indicated for initial management of severe H7N9 pneumonia. Caution should be exercised regarding the use of glucocorticoids, which are not indicated for routine treatment of influenza. Clinical research, including randomized, controlled trials and observational studies, is urgently needed on new antiviral agents, including parenteral neuraminidase inhibitors and drugs with different mechanisms of action, combination antiviral treatment, and immunotherapy. To inform clinical management, rapid clinical data collection, data sharing, analysis, and timely feedback are needed worldwide.[5]

Because H7N9 virus infections have not occurred in humans before, it is expected that persons of all ages might be susceptible worldwide. Serologic assays must be developed so that studies can be conducted to determine whether some people have cross-reactive antibodies to these viruses from prior influenza A virus infections. Existing H7-vaccine viruses are not well matched to this novel H7N9 virus, and extensive efforts are under way to develop potential H7N9 vaccines as quickly as possible. These efforts have started worldwide using the H7N9 sequence data obtained from these early cases, and sharing of H7N9 viruses will further facilitate vaccine development. There are many challenges to making H7N9 vaccines available. Previously studied H7 vaccines were poorly immunogenic in humans, and clinical trials to assess the safety and immunogenicity of H7N9 vaccine candidates will be needed. But even if new vaccine manufacturing technologies, such as tissue-cell-culture–derived vaccine antigens, are utilized, the process from vaccine development to availability will probably take many months.

The 2009 H1N1 pandemic taught us many lessons, including that a pandemic virus can emerge from an animal reservoir in an unexpected location and be spread rapidly through air travel. The focus on critically ill adults early in the pandemic led to elevated public concern about pandemic severity. Clear communication of key messages to the public and the clinical community is

critical in implementing successful prevention and control activities. The detection of human H7N9 virus infections is yet another reminder that we must continue to prepare for the next influenza pandemic. The coming weeks will reveal whether the epidemiology reflects only a widespread zoonosis, whether an H7N9 pandemic is beginning, or something in between. The key is intensified surveillance for H7N9 virus in humans and animals to help answer important questions. We cannot rest our guard.

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Risk, Consent, and SUPPORT

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Comparative effectiveness research has the potential to dramatically improve patient care while reducing costs. In the absence of good evidence about which treatment is best for particular patients, decision making too often hinges on exogenous factors such as advertising and detailing by pharmaceutical companies, what a physician first learned to do, insurance coverage, and local custom. Without good evidence about what is best among competing but generally accepted clinical options, it is often a challenge for physicians to identify the best course of care.

A great deal of effort is under way to make it easier and less expensive to conduct prospective, randomized comparative effectiveness research.[1] Some of the options for conducting such research take advantage of the fact that there is no additional risk to being randomly assigned to one or another equally well-supported treatment option that falls within the standard range of care in clinical practice. This all seems for the good, but there is cause for concern in a recent decision by the Office for Human Research Protections (OHRP) to issue a letter of determination to investigators at the University of Alabama at Birmingham (UAB) about a large multicenter clinical trial to determine appropriate oxygen-saturation levels in severely premature neonates.[2] The OHRP reprimand is troubling both because it has sown confusion and focused unwarranted negative attention on valuable research and because it incorrectly suggests that the risk of comparative effectiveness research involving infants, or any other group, is equivalent to the risk of research involving randomization to a novel intervention.

The UAB case concerns a trial undertaken to determine the appropriate oxygen-saturation levels to use in very premature infants. Among neonatologists, the standard of care varied — too much oxygen was associated with retinopathy of prematurity and possible blindness, but too little oxygen risked neurologic damage and death.[3] By the mid-2000s, neonatologists were calling for research that would help clarify the best oxygen-saturation levels for these patients.[4] Many believed that lower levels would reduce the incidence of retinopathy of prematurity without increasing mortality. The trial, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), randomly assigned patients to higher and lower oxygen-saturation levels within the standard of care.[5]

The OHRP has now found fault with the consent language used when patients were enrolled in SUPPORT. We think it is important to be very clear about the issues at stake here. One is about risk, and the other is about informed consent.

The SUPPORT investigators believed that since all the study infants would receive oxygen levels