Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

www.cdc.gov/flu. Updated information on human infections is available from WHO at http://www.who.int/en.

doi:10.1016/j.annemergmed.2004.10.004

Available online November 19, 2004.

REFERENCES

1. CDC. Cases of influenza A (H5N1)—Thailand, 2004. *MMWR.* 2004;53:100-103.
2. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR.* 2003;53(No. RR-8).
3. Bridges CB, Lim W, Hu-Primmer J, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *J Infect Dis.* 2002;185:1005-1010.
4. Bridges CB, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. *J Infect Dis.* 2000;181:344-348.
5. de Jong JC, Rimmelzwaan GF, Bartelds AI, et al. The 2002/2003 influenza season in the Netherlands and the vaccine composition for the 2003/2004 season [Dutch]. *Ned Tijdschr Geneeskd.* 2003; 147:1971-1975.

COMMENTARY

[Ann Emerg Med. 2005;45:90-92.]

Influenza is one of the costliest infectious diseases worldwide. Not only do yearly endemic outbreaks lead to significant local morbidity and mortality, but less frequent pandemics—4 in the 20th century alone—cause death tolls in the millions. The "Spanish flu" of 1918 to 1919 resulted in 20 to 40 million deaths worldwide.[1] In the late 1990s, after several decades of fairly stable human influenza viruses, highly pathogenic avian influenza infected humans in Southeast Asia for the first time. In the setting of the severe acute respiratory syndrome (SARS) epidemic and emerging human infections with these highly pathogenic avian influenza strains, the prospect of a pandemic looms large for public health authorities and should prompt preparative measures from emergency care providers.

The ability of influenza to cause repeated outbreaks lies in its viral structure and ease of genetic reassortment. Influenza viruses belong to the Orthomyxoviridae family and contain single-stranded RNA. These enveloped viruses can be classified into A, B, and C types on the basis of their internal nucleoprotein and matrix protein identity. Only influenza A and B are associated with major outbreaks.[2] Influenza A is more diverse, associated with more outbreaks, and includes all avian influenza strains.

Influenza A contains 8 distinct genes. Two surface glycoproteins, hemagglutinin and neuraminidase, account for its infectivity as well as trigger the host immune response. Hemagglutinin binds sialic acid receptors on the host cell membrane to gain access to the cell; this is the main target of antibodies and vaccines. Neuraminidase facilitates release of progeny virions from host cells after replication and is the target of antiviral therapies. These proteins are also used to identify different strains; to date, 15 hemagglutinin (H1-15) and 9 neuraminidases (N1-9) have been identified. Only 3 hemagglutinin (H1-3) and 2 neuraminidase (N1, N2) subtypes of influenza A persist in humans. Certain hemagglutinin and neuraminidases subtypes are associated with pigs (H1, H3, N1, N2) and horses (H7, N7, N8). All hemagglutinin and neuraminidase subtypes are established in aquatic birds.[2,3]

The epidemiology of influenza is closely linked with the genetics of these 2 proteins. Local epidemics, like the severe "flu season" of 2003 to 2004 in the United States, are caused by antigenic drift. This means that random point mutations in the genetic sequence escape repair, leading to gradual "drift" of the gene pool. The genes coding for hemagglutinin and neuraminidase are inherently unstable and constantly undergoing genetic drift. People are more susceptible to these slightly altered strains but also retain some degree of crossimmunity from prior influenza exposures. Thus, resultant epidemics are limited in scope and severity.

Antigenic shift is potentially far more dangerous. Shift occurs when 1 of the 8 genes is exchanged in its entirety for another during replication. This requires a host cell, called a "mixing vessel," to be coinfected with 2 influenza strains. Pigs are an ideal mixing vessel because they are readily infected with both human and avian forms.[4,5] Alternatively, a person infected with a conventional human influenza virus could be coinfected with a highly pathogenic avian influenza strain. Global influenza pandemics result from such antigenic shift because there is no pre-existing immunity to the new strain.

Aquatic birds serve as the primary reservoir for influenza A, carrying the viruses largely without adverse effects.[4,6] Domestic poultry, however, are highly susceptible to avian influenza. Depending on the virulence of the particular strain, poultry may manifest mild upper respiratory infections or rapidly fatal illness.[4] Formerly known as "fowl plague," highly pathogenic avian influenza is now identified as strains H5 and H7, which cause severe disease in terrestrial birds.[6,7]

Since the Hong Kong pandemic of 1968, the human strains of influenza A had remained fairly stable.[5] However, in the late 1990s, new avian strains began to infect humans in relatively small numbers. Eighteen people were infected with influenza A (H5N1) in Hong Kong in 1997; 6 died.[4,8] In 1999, H9N2 was isolated for the first time from 2 children in Hong Kong, who both recovered after mild respiratory illnesses.[4,8] Most concerning, however, is this year's re-emergence of influenza A (H5N1)—slightly different genetically than the 1997 strain.[9-11] Affecting poultry across Southeast Asia, this is the most widespread outbreak of avian influenza in history. More than 100 million poultry have died or been killed as a result.[12] As of September 28, 2004, in Thailand and Vietnam, 42 cases were reported in healthy young adults and children, with a 71% mortality rate.[13]

The H5N1 strain of influenza transmitted to humans this year has 2 of the 3 classic features of a potential pandemic: high mortality and an immunologically naive population.[14] Lacking,

up to this point, is efficient human-to-human transmission.[5] Of note, some evidence shows limited human-to-human spread during the 1997 Hong Kong outbreak. A case-control study of health care workers in 3 hospitals caring for infected patients showed that more exposed health care workers were seropositive for H5N1 antibodies than nonexposed workers (3.7% versus 0.7%).[15] None exhibited signs of illness.

The clinical presentation of highly pathogenic influenza A (H5N1) includes fever, cough, and shortness of breath. Sputum production, pleuritic chest pain, and diarrhea were variably present.[4,10,11] Almost all patients had contact with poultry; the mean incubation period was 3 days.[4,10] On examination, tachypnea, respiratory distress, and rales were found in the first 10 patients in Vietnam;[10] a similar but less dramatic presentation was found in the patients in Thailand.[11] In all, the chest radiographs were markedly abnormal: patchy or interstitial infiltrates, lobar collapse, focal consolidation, or air bronchograms.[10,11] Laboratory testing revealed leukopenia (2,100/mm^3) with pronounced lymphopenia (700/mm^3), with an inversion of the CD4:CD8 ratio.[10,11] Some patients also exhibited thrombocytopenia and elevated transaminases.

The natural history of influenza A (H5N1) is one of progressive respiratory distress and multiple organ system involvement. The H5N1 strain, more so than others, directly infects macrophages and causes excess cytokine release.[2,4] This creates a clinical picture akin to systemic inflammatory response syndrome. At the same time, H5N1 is resistant to the antiviral action of these excess cytokines.[16] Also unique to influenza A strain H5N1 is its propensity to affect other organ systems, renal, hematologic, and gastrointestinal in particular.[6]

In the acute setting, definitive diagnostic testing is not yet available. Rapid nasopharyngeal antigen assays can quickly identify the presence of influenza A but cannot differentiate between strains. Reverse transcriptase polymerase chain reaction is the diagnostic test of choice for viral typing but is not helpful acutely, as results require 10 to 14 days. This test may be available through the local health department or by calling the Centers for Disease Control and Prevention (404-639-3747).

Two basic classes of antiviral agents are available for the management of influenza A, M2 membrane protein inhibitors, amantadine and rimantadine, and neuraminidase inhibitors, zanamivir and oseltamivir. These agents reduce the severity and duration of symptoms when initiated within 2 days of symptom onset.[2] These antiviral medications have not been well studied for avian influenza but may play a role in preventing concomitant human and avian influenza infection. The current H5N1 avian strain is resistant to M2 protein inhibitors.[4,9,11] Neuraminidase inhibitors, steroids, and broad-spectrum antibiotics were variably used in the recent H5N1 outbreaks. Given the relatively small number of patients and the completely uncontrolled manner in which the medications were used, however, no conclusions can be drawn regarding their efficacy. Influenza vaccination appears to be the most logical method of controlling the spread and prevent potential epidemics, but current vaccines provide no protection against avian H5 or H7 strains. Because H5 and H7 strains are highly lethal to chicken embryos, current vaccine production methods cannot produce avian vaccine efficiently. Newer vaccine production techniques, including the use of reverse genetics technology that can tailor rapidly to specific influenza strains, appear to be promising.[17]

Full respiratory isolation precautions, similar to those for SARS, are recommended in all cases of suspected human infection with highly pathogenic avian influenza viruses. These include hand washing, gloves and gown, N95 masks, eye protection, and a negative pressure isolation room, if available. Those discharged home should be isolated in the home setting, as is recommended for SARS. These precautions should be continued for 14 days after onset of symptoms until an alternative diagnosis is established or test results indicate the patient is not infected with influenza A. The diagnosis of influenza A H5N1 should be considered and isolation precautions instituted for any patient with respiratory symptoms and either contact with poultry or recent travel to Southeast Asia.

Because a definitive diagnosis of highly pathogenic avian influenza cannot be made in the emergency department and these patients will appear ill, treatment should be initiated early and broadly. Antibiotics for severe pneumonia would be appropriate, as well as antiviral agents. Nasopharyngeal swabs for influenza A should be sent and blood drawn for reverse transcriptase–polymerase chain reaction typing (contact the local health department). Lastly, for both testing and surveillance purposes, the health department should be contacted for all suspected cases.

It is important for those involved in disaster planning to incorporate large-scale infectious outbreaks into their preparations. Bioterrorism, SARS, and pandemic influenza represent threats that could quickly overwhelm our health care system. Preparations should include infection control plans for rapid influx of infectious patients into health care facilities, personal protective equipment for health care workers, and access to stockpiles of antimicrobials, vaccines, and supportive care equipment.

doi:10.1016/j.annemergmed.2004.10.005

Available online November 19, 2004.

REFERENCES

1. Taubenberger JK, Reid AH. The 1918 "Spanish" influenza pandemic and characterization of the virus that caused it. In: Potter CW, ed. *Influenza*. Amsterdam, The Netherlands: Elsevier; 2002:101-122.
2. Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet*. 2003; 362:1733-1745.
3. Horimoto T, Kawaoka Y. Pandemic threat posed by avian influenza A viruses. *Clin Microbiol Rev*. 2001;14:129-149.
4. Trampuz A, Prabhu RM, Smith TF, et al. Avian influenza: a new pandemic threat? *Mayo Clin Proc*. 2004;79:523-530.

5. Claas EC, Osterhaus AD, van Beek R, et al. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *Lancet.* 1998;351:472-476.
6. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet.* 1998;351:467-471.
7. Capua I, Alexander DJ. Avian influenza and human health. *Acta Tropica.* 2002;83:1-6.
8. Peiris M, Yuen KY, Leung CW, et al. Human infection with influenza H9N2. *Lancet.* 1999;354:916-917.
9. CDC. Outbreaks of avian influenza A (H5N1) in Asia and interim recommendations for evaluation and reporting of suspected cases—United States, 2004. *MMWR Morb Mortal Wkly Rep.* 2004;53:97-100.
10. Hien TT, Liem NT, Dung NT, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med.* 2004;350:1179-1788.
11. CDC. Cases of influenza A (H5N1)—Thailand, 2004. *MMWR.* 2004;2004(53):100-103.
12. CDC Health Update: Update on Avian Influenza A (H5N1). August 12, 2004. Available at: http://www.cdc.gov/flu/avian/professional/han081304.htm. Accessed August 14, 2004.
13. World Health Organization Web site. Confirmed human cases of avian influenza A (H5N1). Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2004_09_28/en/print.html. Accessed September 29, 2004.
14. Barclay WS, Zambon M. Pandemic risks from bird flu. *BMJ.* 2004;328:238-239.
15. Bridges CB, Lim W, Hu-Primmer J, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *J Infect Dis.* 2002;185:1005-1010.
16. Seo SH, Hoffmann E, Webster RG. Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. *Nat Med.* 2002;8:950-954.
17. Palese P, Garcia-Sastre A. Influenza vaccines: present and future. *J Clin Invest.* 2002;110:9-13.