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REVIEW

Avian flu: What the otolaryngologist needs to know

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Based on historic patterns an influenza pandemic is inevitable. An influenza virus pandemic occurs on average, three to four times each century when new virus subtypes emerge and are transmitted readily from person to person. The recent avian influenza A (H5N1) virus outbreak in Southeast Asia has heightened our concern that a disaster may be imminent.

The influenza pandemic of 1918 spread around the world, killing 40 to 50 million people in less than 1 year.[1] In 1918 it was the "Spanish Flu;" today it's the "chicken flu," "bird flu," or "avian flu." It is not completely understood how the H1N1 virus of 1918 led to so much death. It has been suggested recently that the virus may have spread directly from birds to humans.[2] In fact, a recent study of the 1918 influenza polymerase gene sequences, suggests this virus was very likely derived from an avian source and it seems to have some very similar characteristics to the present H5N1 virus.[3] The years 1957 and 1968 brought two more influenza A pandemics. Viral isolates from these outbreaks contained components of both human and avian influenza viruses, reinforcing the idea that pandemics occur after a mixing of two formerly species-specific influenza viruses in a host susceptible to both strains. Little is known about the best way to respond to an inevitable influenza pandemic.

Influenza A viruses infect a variety of animals including humans, marine mammals, pigs, horses, and birds. Influenza viruses are classified in terms of the species being infected (ie, human or avian) and the particular hemagglutinin and neuraminidase present in the virus. Every influenza A subtype characterized currently (hemagglutinins H1 to H15 and neuraminidases N1 to N9) have been found in birds.[4,5]

The recent avian influenza A (H5N1) outbreak is concerning for several reasons, not only due to its high mortality rate, but also the relative predominance of young adults and children being affected (Figs 1-4). Patients infected with H5N1 may present with a constellation of symptoms including some that may present to the otolaryngologist's office. Reported symptoms have included pharyngitis, nasal congestion, rhinitis, cough, cervical lymphadenopathy, and conjunctivitis. This review is aimed at educating the otolaryngologist of the potential for an avian flu pandemic and how to recognize and diagnose potential cases of H5N1.

EPIDEMIOLOGY

Humans are not typically susceptible to avian-specific influenza viruses. The 1997 Hong Kong outbreak of avian influenza A (H5N1) marked the first documented account of human infection with an avian-specific influenza virus. This first outbreak resulted in severe disease in 18 humans, of which six were fatal. This particular outbreak took place concurrently with an outbreak of the same strain of virus in the poultry population of Hong Kong.[6] Scientists determined that all cases had had close contact with infected poultry. Further genetic studies showed that in all likelihood, the virus had jumped directly from birds to humans.[6] Quick response by Chinese authorities led to the destruction of Hong Kong's entire poultry population (around 1.5 million birds). This may have avoided a global influenza pandemic.

Since its first outbreak in Hong Kong, the H5N1 virus has expanded its geographic range. Indonesia, Viet Nam, Thailand, Cambodia, China, Turkey, and Iraq have all had confirmed human cases. Now more recently, Russia and Kazakhstan have reported outbreaks of Avian Influenza (H5N1) in poultry. Migratory wild bird deaths have been reported and many of these have been found to be infected with the H5N1 virus as well. It

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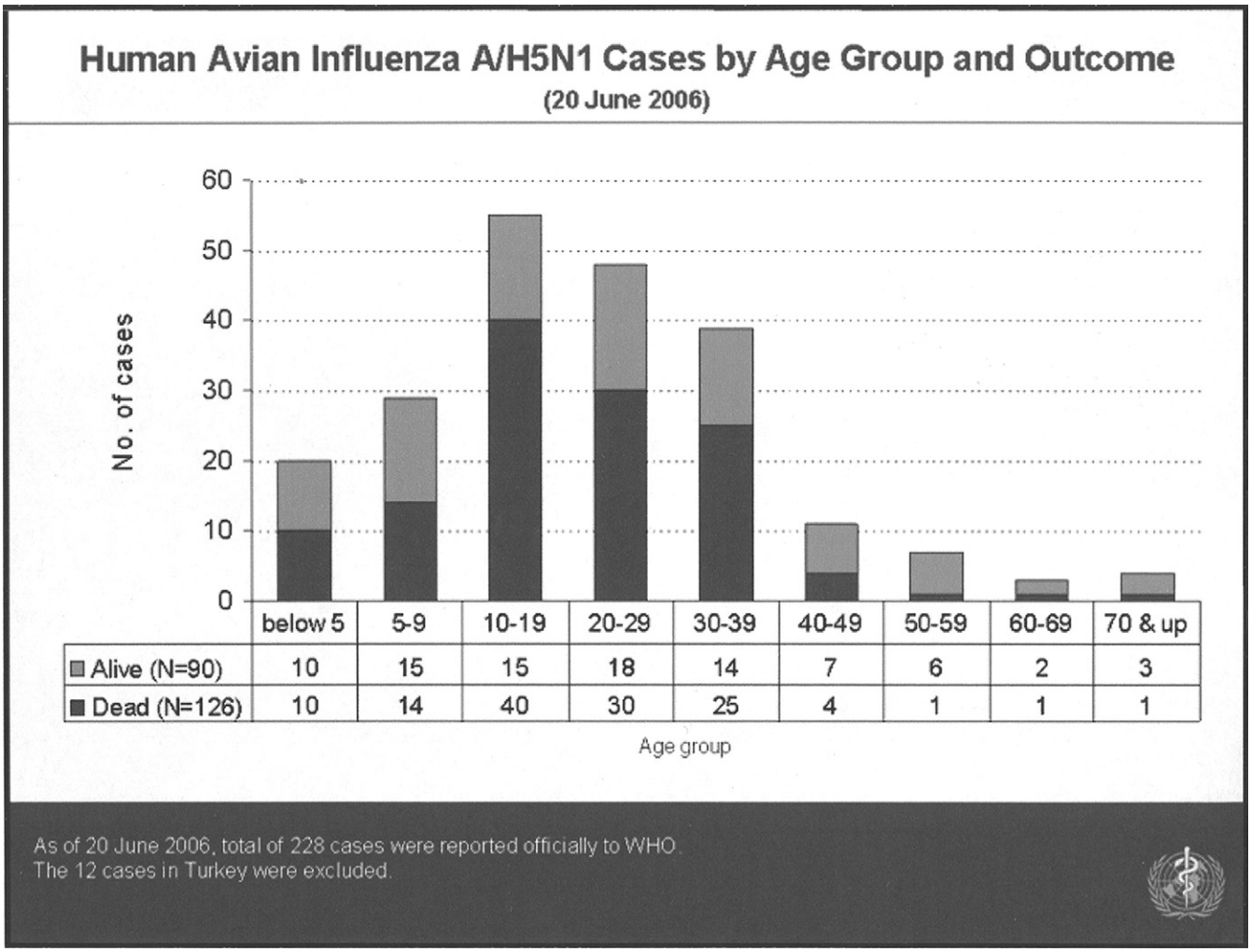

Figure 1 Total number of cases includes number of deaths. WHO reports only laboratory-confirmed cases. Reproduced from World Health Organization. Cumulative number of confirmed human cases of Avian Influenza A/(H5N1) reported to WHO. Available at: www.who.int/csr/disease/avian_influenza/country/cases_table_2006_03_24/en/index.html. Accessed July 1, 2006.

is thought that the spread to Europe may be attributed to contact between domestic poultry and wild waterfowl through the sharing of common water sources.[7]

Almost all human cases had known contact with poultry.[8-10] Infected individuals have been, for the most part, previously healthy adults and children. This is one of the most concerning features of these outbreaks—the high mortality rate in young, healthy individuals.

VIROLOGY

The influenza viruses are enveloped RNA viruses. Influenza A viruses are found in many animals besides humans, including birds, pigs, whales, horses, and seals; whereas Influenza B viruses circulate mainly among humans. Influenza A viruses are classified into subtypes based on the species of origin and two viral surface glycoproteins, hemagglutinin (H) and neuraminidase (N). There are 15 different characterized subtypes of hemagglutinin and 9 subtypes of neuraminidase. However, only viruses with three of the hemagglutinin subtypes have been involved in widespread human infections (H1, H2, and H3).

Wild birds are thought to be the natural reservoir for all subtypes of influenza A viruses. Most birds infected with influenza viruses are asymptomatic; however, infection with some high pathogenic avian influenza A viruses (for example, some strains of H5 and H7 viruses) cause severe disease and death among species of wild and domestic birds like chickens, pigeons, and turkeys.[11]

Influenza A viruses are genetically unstable and thus have multiple different mechanisms to avoid host defense. The two main mechanisms Influenza A viruses employ to keep their genetic information in flux are known as antigenic "drift" and antigenic "shift."

The first mechanism, antigenic "drift," is a result of the lack of an efficient proofreading mechanism and repair of errors that may occur during viral replication. The uncorrected errors result in changes in the genetic composition of the viruses. These changes occur as the virus replicates within a single

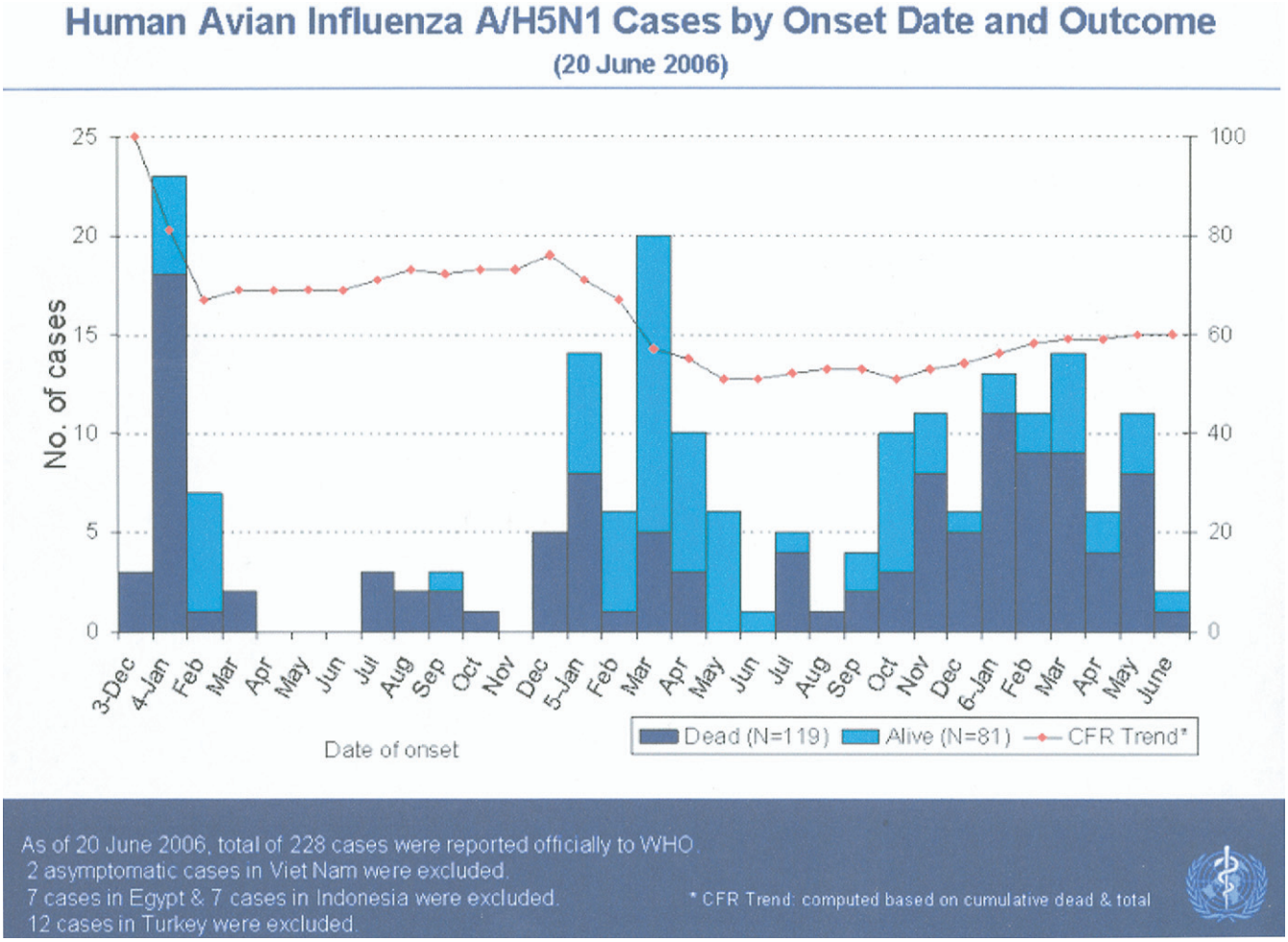

Figure 2 Reproduced from World Health Organization Regional Office for the Western Pacific. Communicable disease surveillance and response. Available at: www.wpro.who.int/sites/csr/data/graphs1.htm. Accessed July 1, 2006.

species. When this occurs, a new antigenic variant is born. These constant changes help the virus elude host defense mechanisms.

The influenza viruses have a second concerning characteristic. Influenza A subtypes from different species can swap genetic material and merge. The reassortment process is known as antigenic "shift." Antigenic "shift" results in unique subtypes different from the parent viruses. Hosts will have not been exposed previously to these unique viruses; therefore, they will not possess immunity to the new subtypes. Existing vaccines may not offer protection from novel viruses either. It is thought that antigenic shift has resulted in lethal pandemics in the past. If this were to happen to an avian-specific virus such as H5N1, the unique subtype would possess genes from human influenza viruses that make it readily transmissible from person to person for a lasting period of time.

Historically, pigs were thought to be the "test tube" in which antigenic "shift" occurs. Both avian and mammalian viruses can infect pigs readily (Fig 5). Therefore, the viruses are thought to mix with each other within pigs. It is thought that in Southeast Asia, where humans live and interact in close proximity to poultry and pigs, the environment may be favorable for antigenic shift to occur. More recently researchers have suggested that for some avian influenza viruses, humans themselves may serve as the "test tube" in which mixing may occur.[6] That is, if a human is concurrently infected with both an avian influenza A virus and a human strain, the two may mix and produce a novel strain more easily transmitted among humans. If such a mixing were to occur with a high pathogenic strain, such as H5N1, the results may be a global pandemic.

These mechanisms result in frequent and permanent antigenic changes in influenza viruses, which necessitates constant monitoring of global influenza virus infections by both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). This facilitates warranted adjustments made to influenza vaccines.[6]

TRANSMISSION

The main route of transmission of H5N1 is thought to be through either direct contact with infected birds or surfaces contaminated by their excrement. It has been shown that

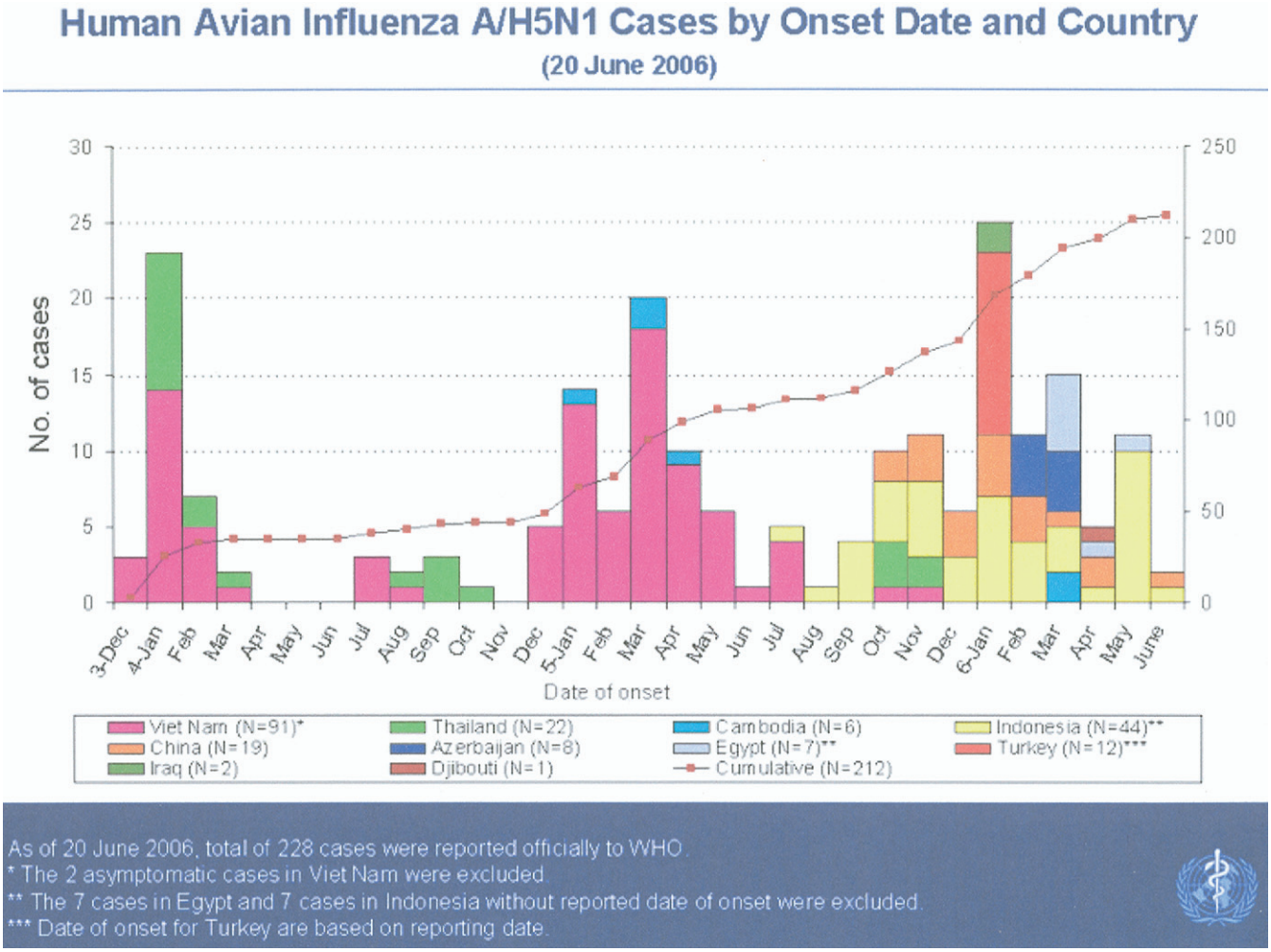

Figure 3 Reproduced from World Health Organization Regional Office for the Western Pacific. Communicable disease surveillance and response. Available at: www.wpro.who.int/sites/csr/data/graphs1.htm. Accessed July 1, 2006.

afflicted birds that survive may excrete virus for at least 10 days in their feces.[6] The infection seems to be passed along between both domestic birds and migratory wild birds. Transmission of viruses from animals to humans depends on the characteristics of the pathogen, the concentration of infected host animals, and how often humans come in contact with the infected hosts.[12] In large portions of Southeast Asia, it is common practice for whole households to live and work in very close contact with poultry and other animals. Because the avian influenza A (H5N1) virus is known to be transmitted through contact with infected bird oral secretions and feces, these close living relationships facilitate interspecies transmission. Eating properly cooked poultry or eggs cannot transmit avian influenza viruses.

Besides a single case report, to date there has been very little evidence for any human-to-human transmission.[13] As more humans become infected, however, the likelihood of coinfection with H5N1 and another human-specific influenza A strain increases. It is possible the two viruses may mix and result in the emergence of a novel subtype with the ability to be easily transmitted within the human population.[6]

PATHOPHYSIOLOGY

There is limited published information about the clinical course of human infection with avian influenza A (H5N1). However, the cases published have reported the clinical presentation of a typical influenza-like illness with evidence of pneumonia. Patients developed symptoms including fever, cough, sore throat, conjunctivitis, myalgias, and dyspnea. In some outbreaks, specifically the Hong Kong outbreak in 1997, gastrointestinal manifestations, including abdominal pain, vomiting, and diarrhea were prominent.[4] However, more recent outbreaks have been lacking predominant gastrointestinal manifestations.[14] In one study, symptom onset tended to occur two to four days after exposure to presumed infected birds.[9] In several of the fatal cases, severe respiratory distress leading to acute respiratory distress syndrome (ARDS) ensued secondary to viral pneumonia.[4,9,10,14] Previously healthy adults, children, and some with chronic medical illnesses, were affected. Leukopenia on presentation may be the most significant adverse prognostic indicator.[4,9,14] As of January 2006, the mortality rate was approximately 55% (Fig 1).[15] Mortality of infection

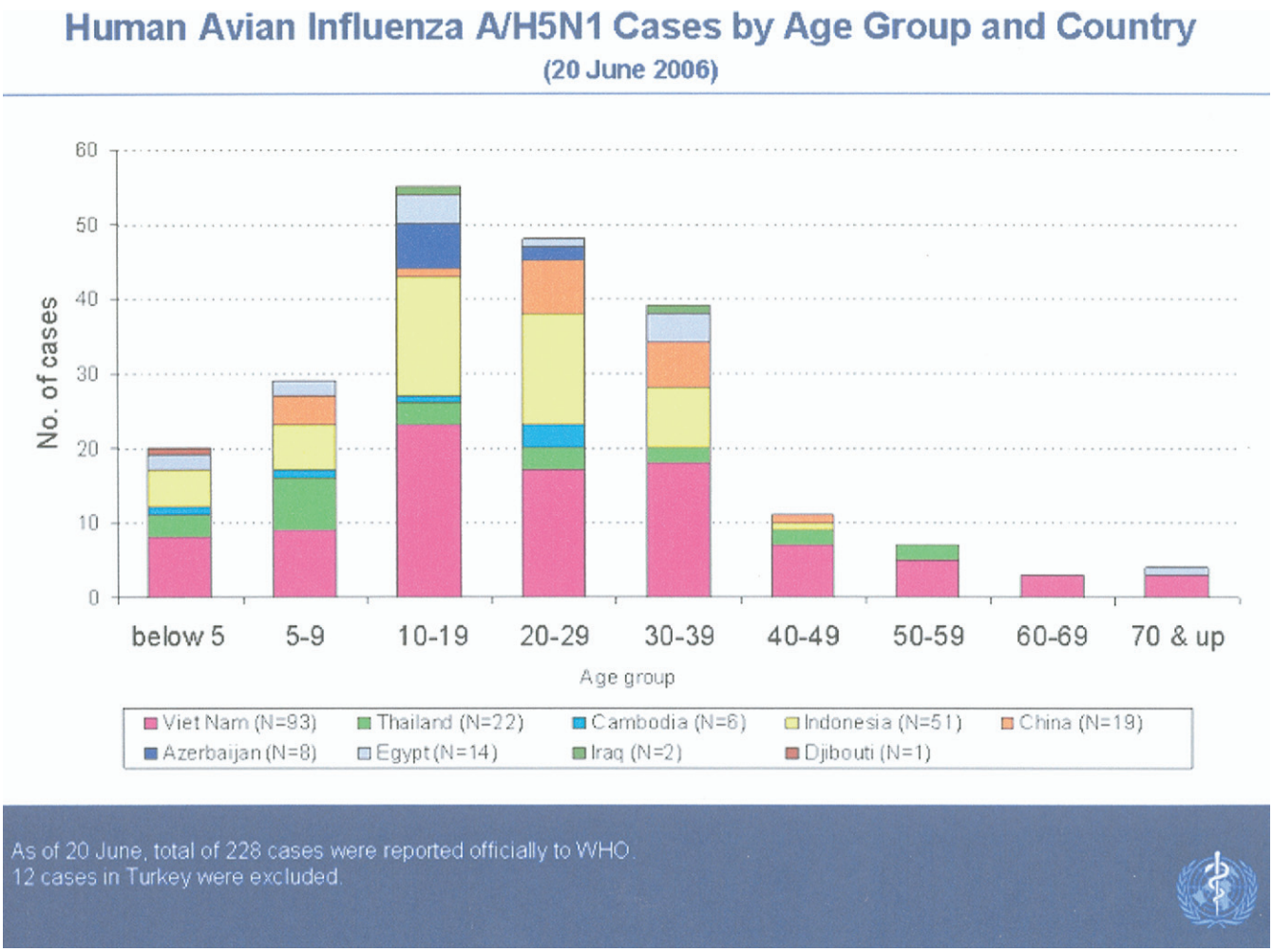

Figure 4 Reproduced from World Health Organization Regional Office for the Western Pacific. Communicable disease surveillance and response. Available at: www.wpro.who.int/sites/csr/data/graphs1.htm. Accessed July 1, 2006.

does not respect any age boundaries (Fig 1) One published report of five individuals having confirmed infections with H5N1 in Thailand in 2004 described the clinical course of four male children (ages 6 to 7) and one female adult (age 58). None had preexisting illnesses; all succumbed to the infection. They presented with symptoms including fever,

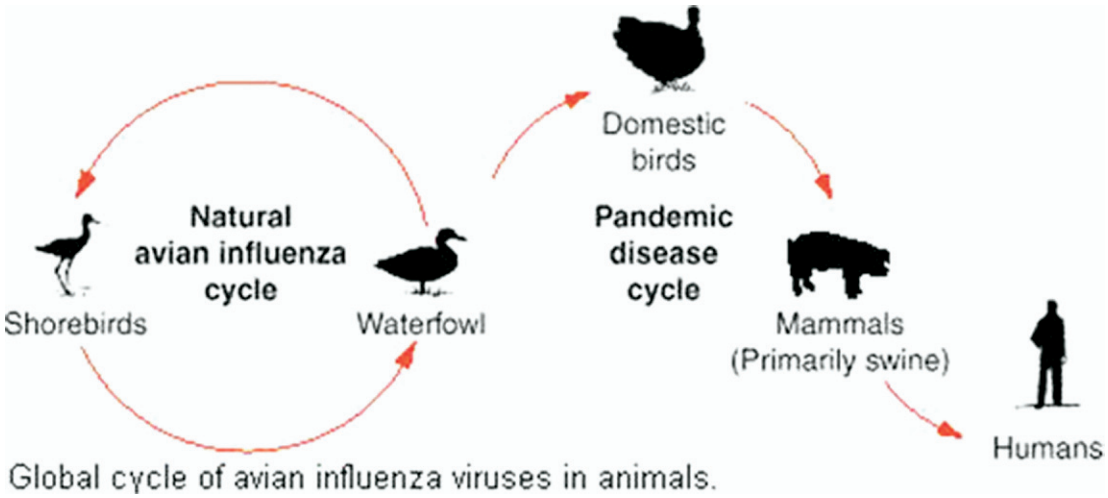

Figure 5 Reproduced from U.S. Army Center for Health Promotion and Preventive Medicine website. Available at: chppm-www.apgea.army.mil. Accessed October 29, 2005.

sore throat, rhinorrhea, cough, myalgias, and dyspnea. They were admitted to a hospital on days two through six after onset of symptoms. All experienced respiratory failure and required intubation at a median of seven days (range, 4 to 10 days) after onset of illness. Three of the children died two to four weeks after onset of symptoms, and one child and the adult died eight days after onset of symptoms.[14]

One theory explaining the high mortality rate, especially in the young and previously healthy, is a pronounced activation of the immune response. This leads to activation of the proinflammatory cytokine cascade and inflammatory response contributing to tissue damage. Most fatal cases have had evidence of multisystem organ failure and ARDS.[16]

Symptoms of more common human influenza viruses begin two to three days after exposure to the virus with an acute febrile respiratory illness including cough, headache, fatigue, and myalgia for three to four days, and symptoms may persist for up to two weeks. Subsequent symptoms may include pharyngitis, nasal congestion, rhinitis, cough, cervical lymphadenopathy, conjunctivitis, and sometimes gastrointestinal symptoms. At-risk patients may progress to pneumonia and shock. However, the avian influenza A (H5N1) infection seems to be much more aggressive and fast acting than the typical human influenza infection, progressing to respiratory distress within a few days of onset of symptoms.[4,9,10,14]

LABORATORY AND DIAGNOSTIC MEASURES

Clinical presentation of fever, cough, sore throat, dyspnea, and chest radiograph abnormality along with any exposure to poultry should raise the suspicion of possible avian influenza infection. Reliable viral isolation studies for respiratory specimens are available for diagnosing influenza strains of animals and humans. The two main assays that are used for detecting avian influenza A strains are reverse transcriptase polymerase chain reaction (RT-PCR) and viral cultures. The best specimen for the assays is a nasopharyngeal aspirate or swab isolated within three days of onset of symptoms.[4,17,18] Many laboratories have the necessary high-containment facilities and reagents for performing these tests as well as the appropriate experience.[6] There is no rapid office based assay for avian influenza A (H5N1).

According to the CDC, specific testing for avian influenza A (H5N1) virus is indicated for hospitalized patients with:

1. Respiratory illness including radiographically confirmed pneumonia, ARDS, or other severe respiratory illness for which an alternate diagnosis has not been established, and,
2. Travel history significant for travel to a country with documented avian influenza A (H5N1) cases either in animals or humans, within 10 days of onset of symptoms (for a regularly updated listing of countries with documented H5N1 cases, see the WHO website (www.who.int).[17]

Testing should be considered on a case-by-case basis in consultation with local and state health authorities for ambulatory or hospitalized patients with all of the following:

1. Temperature >38°C (101.4°F), and,
2. Cough, sore throat, shortness of breath, and,
3. History of contact with poultry or possible human case of Influenza A (H5N1) within 10 days of onset of symptoms.[17]

Samples may be sent to the CDC for evaluation, if the patient meets the above criteria.

For information or advice contact the CDC contact center by telephone at 1-800-CDC-INFO, email at coca@cdc.gov, or visit the CDC Avian Influenza website at www.cdc.gov/flu/avian/professional.

TREATMENT

Full droplet and respiratory infection control measures should be implemented early in any suspected outbreak (Table 1). Supportive care, prophylactic antibiotics, and select antiviral medications are the only available treatments to date.

Four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine (Flumadine, Forest Pharmaceuticals, Inc, St. Louis, MO), zanamivir (Relenza, Glaxo Wellcome, London, United Kingdom), and oseltamivir (Tamiflu, F. Hoffman-La Roche Ltd Pharmaceuticals Division, Basel, Switzerland). Amantadine and rimantadine are effective against type A influenza virus only, the type that H5N1 belongs to. However, testing of human isolates from H5N1 infected patients has shown resistance to amantadine and rimantadine; therefore, treatment with neuraminidase inhibitors (zanamivir or oseltamivir) should be initiated early.[17] There has been a report of an H5N1 isolate resistant to oseltamivir in Viet Nam.[16]

There have been no controlled clinical trials to study the efficacy of neuraminidase inhibitors for the treatment of human avian influenza infections. The use of these medications for avian influenza infections is based on animal experiments where they have been shown to decrease mortality from H5N1 infections.[16] There is anecdotal evidence that initiation of treatment with neuraminidase inhibitors early may decrease mortality in human infections.[18]

Stockpiling or hoarding of these medications may lead to public health problems and inability to distribute medications to areas of need. The health authorities have plans to ensure distribution of these medications to areas of need if epidemics arise.

Table 1
Interim recommended infection-control precautions* for influenza A (H5N1)

- All patients with a febrile respiratory illness should be asked about their recent travel history and managed using *Respiratory Hygiene/Cough Etiquette in HealthCare Settings* guidelines.†
- Isolation precautions for all hospitalized patients who have or are under evaluation for influenza A (H5N1) are the same as those that should be used for severe acute respiratory syndrome (SARS), as follows:
  - Pay careful attention to hand hygiene before and after all patient contact.
  - Use gloves and gown for all patient contact.
  - Wear eye protection when within 3 feet of the patient.
  - Place the patient in an airborne isolation room (i.e., monitored negative air pressure in relation to surrounding areas with six to 12 air changes per hour).
  - When entering the patient's room, use a fit-tested respirator at least as protective as an N95 filtering-facepiece respirator approved by the National Institute for Occupational Safety and Health.
- Outpatients or hospitalized patients discharged in <14 days should be isolated in the home setting on the basis of principles for home isolation of SARS patients.§
- These precautions should be continued for 14 days after onset of symptoms until an alternative diagnosis is established or diagnostic test results indicate that the patient is not infected with influenza A virus.

*Additional information about health-care isolation precautions is available at http://www.cdc.gov/ncidod/hip/isolat/isolat.htm.
†Available at http://www.cdc.gov/flo/professionals/infectioncontrol/resp hygiene.htm.
§Available at http://www.cdc.gov/ncidod/sars/guidance.

PREVENTION

Although specific H5N1 vaccine development is underway, none is available currently. Probably the two highest yield measures for prevention of an H5N1 pandemic are to stop epidemics within avian populations and vaccination of persons at high risk of exposure to infected poultry with existing influenza vaccines. These two measures would decrease human exposure to H5N1 and decrease likelihood of mixing of H5N1 with human-specific viruses. The WHO specifically recommends workers involved in the culling of poultry flocks take protective measures to decrease exposure to bird excrement. Protective clothing and gear as well as proper cleaning of surfaces must be employed. The WHO also reports that poultry workers in areas with outbreaks should receive antiviral drugs as prophylaxis. Proper reporting to local and state officials is a must when cases of avian influenza are found in humans. Public health is dependent on the dissemination of pertinent information. Officials need to assess the virology of circulating animal and human infections to best assess vaccination needs and other protective measures.[6]

To date there has been no evidence of efficient human-to-human transmission of H5N1 virus. However, the continued circulation and now spread to Europe of the virulent H5N1 virus increases the possibility of the reassortment of this virus with other circulating human influenza A strains and increases the possibility of a global influenza pandemic. Increasing efforts to control poultry outbreaks and increased surveillance among poultry and humans needs to be of utmost priority.

CONCLUSION

Future influenza pandemics leading to widespread morbidity and mortality may be inevitable. As documented in Southeast Asia over the past nine years, the avian influenza A (H5N1) virus clearly has the ability to cross between species and result in devastating illness in humans. Infected patients present with a multitude of symptoms, including head and neck symptoms. For this reason clinicians, including otolaryngologists, should be aware of the clinical features of the Influenza A (H5N1) disease in humans and the potential risk factors for infection. Prompt identification of potential H5N1 cases is essential to ensure that patients can be managed appropriately, healthcare workers are protected, and widespread outbreaks can be thwarted.[19-32]

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