

## Avian H5N1 Influenza—Are We Inching Closer to a Global Pandemic?

Avian influenza or “bird flu” first moved from being an obscure disease known only to veterinarians to a widely recognized global health issue in 1997 when an outbreak caused by the H5N1 strain of the influenza A virus was reported in poultry being sold in the huge live animal markets of Hong Kong. While outbreaks of avian influenza in domestic poultry and other birds are common, the uniqueness of this outbreak was the fact that, for what was thought to be the first time, there was documented transmission of a virulent avian influenza virus to humans.<sup>1</sup> The virus resulted in respiratory illness in 18 previously healthy adults, 6 of whom died. All cases occurred in persons who had close contact with infected poultry, and there was no documented human-to-human transmission of the virus. The outbreak was controlled by culling the entire poultry population of Hong Kong.

The virus reemerged as an important pathogen in 2003 when another avian influenza outbreak, unprecedented in scale and geographic extent, affected poultry in multiple Asian countries, including Cambodia, China, Indonesia, Japan, Laos, South Korea, Thailand, and Vietnam.<sup>2</sup> Paralleling disease in poultry, since December 2003 human cases of H5N1 avian influenza have been reported in 3 waves. The first resulted in 35 cases and 24 deaths in Vietnam and Thailand between December 2003 and October 2004. The second, which again involved Thailand and Vietnam, consisted of 9 cases, 8 of which were fatal, in July and August 2004. The third and largest wave began in December 2004 and as of November 8, 2005, has resulted in 80 human cases and 31 deaths in Indonesia, Vietnam, Thailand, and Cambodia, with most cases occurring in Vietnam.<sup>2</sup>

Since the review on avian influenza published in *Mayo Clinic Proceedings* in April 2004,<sup>3</sup> new developments seem to have brought us closer to an influenza pandemic caused by the H5N1 virus. The avian influenza epidemic has made its way out of Southeast Asia, with infected birds now being reported as far north as Mongolia and Siberia and as far west as Croatia. The number of human cases continues to rise, with the current total case count as of November 8, 2005, at 124 laboratory-confirmed cases.<sup>4</sup> Mortality in infected patients remains high, approximately 50% (Table 1), despite the fact that most cases have occurred in young healthy adults. At least 1 report has

pointed to person-to-person transmission.<sup>5</sup> The virus has also increased its host range, with fatal cases reported in tigers and domestic cats.<sup>6-8</sup> At the same time, a recent report documented the detection of an oseltamivir-resistant H5N1 strain from Vietnam.<sup>9</sup>

Perhaps most chillingly, the genome of the influenza A virus responsible for the largest documented influenza pandemic on record—the Great Influenza Epidemic of 1918 (the “Spanish Flu”)—was recently sequenced and found to be *entirely* of avian origin, making the 1918 pandemic the first confirmed bird flu outbreak in humans.<sup>10</sup> This means that genetic reassortment—the intracellular mixing and genetic recombination of bird and human influenza viruses thought to be the precursor to the 1957 and 1968 pandemics—may not be necessary for influenza viruses to acquire the capacity to efficiently infect humans. By adaptive mutation, avian influenza viruses appear to have the capacity to become highly pathogenic to humans and also readily transmissible between humans, both of which are essential for a pandemic to occur. The final prerequisite for pandemic disease—a global population with no immunity to the virus—already exists.

On the brighter side, human-to-human transmission of H5N1 avian influenza remains very limited. An experimental avian vaccine has shown a high level of protection in chickens.<sup>11</sup> At least 1 candidate human vaccine against H5N1 avian influenza is in clinical trials. Initial reports indicate that the vaccine is safe and immunogenic in healthy adults, although only at high antigen levels.<sup>12</sup> Further trials incorporating an adjuvant to reduce the quantity of antigen needed are under way.

The World Health Organization<sup>2,13</sup> and governments across the globe are now keenly aware of the possibility of a pandemic and are actively preparing by (1) investing in vaccine development, (2) stockpiling neuraminidase inhibitor antiviral drugs (see subsequent discussion), and (3) perhaps most importantly, planning at both national and local levels to be ready to care for very large numbers of ill persons and, as appropriate, mass dispense vaccines and antiviral drugs.<sup>14</sup> Consistent with these goals, the US Department of Health and Human Services just released its long-awaited *National Strategy for Pandemic Influenza*.<sup>15</sup>

Despite all this activity, is the world any better prepared today to deal with a pandemic than in 1918? If a H5N1 pandemic were to occur this winter, would we have a vaccine, have enough antiviral drugs, or be ready to provide the medical care for the hundreds of millions who would become infected and ill? The answer almost certainly is *no*. However, epidemiological modeling stud-

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ies<sup>16,17</sup> suggest that combining geographically targeted antiviral prophylaxis with “social-distancing measures”—closing schools and workplaces and establishing quarantine zones—would likely be effective in containing an epidemic in its earliest stage, but only if we could ensure the following.

1. Very early identification of the index case cluster, with efficient ongoing surveillance for new cases

2. Sufficient stockpiles of antivirals, with the capacity for rapid delivery of antivirals to the target groups for prophylaxis

3. Rapid institution and enforcement of quarantine measures and a high level of compliance with these measures on the part of the target population

4. International cooperation with all the above strategies, including travel restrictions and, perhaps most importantly, sharing of national antiviral stockpiles<sup>18</sup>

Even if these strategies do not curtail the pandemic, it may be possible to buy the rest of the world precious time to better prepare by ramping up production of vaccine and antivirals, both of which could save millions of lives. In the pre-SARS (severe acute respiratory syndrome) era, achieving the necessary cooperation in containment strategies (such as those listed previously) would have been deemed unrealistic, unprecedented, and highly unlikely to happen. Our success in controlling SARS (ie, a communicable respiratory illness with high mortality, no effective treatment or vaccine, and multiple established foci of disease all over the world) purely through public health measures demonstrates that when the stakes are high, international cooperation in public health can be achieved.<sup>18,19</sup> If we have pandemic avian influenza, the stakes will never have been higher.

Viewing the continued spread of the avian H5N1 virus over the past months from a dozen Southeast Asian countries to Siberia, Kazakhstan, Turkey, Romania, and Croatia, we believe that it is only a matter of time until the virus will be detected in North American birds. This should be anticipated and publicly acknowledged to prevent panic. However, these conditions do not mean that epidemic or, especially, pandemic human disease is imminent, considering that since 2003 more than 100 million domestic and wild birds have been infected throughout Asia and these birds lived among several billion humans, including many rural farmers who have been in direct contact with infected birds. Despite this, less than 130 human cases have been reported to date, nearly all in individuals with very close and prolonged contact with birds. Moreover, there have been no documented human cases outside of the cluster of affected Southeast Asian countries. It must be reemphasized that major genetic alterations in the virus will have to occur before rapid human-to-human spread—vis-à-vis epidemic and, ultimately, pandemic disease—is likely to occur.

TABLE 1. Number of Confirmed Human Cases of Avian Influenza Reported to the World Health Organization as of November 8, 2005<sup>4</sup>

Country	Cases	Deaths	Mortality (%)
Vietnam	91	41	45
Thailand	20	13	65
Cambodia	4	4	100
Indonesia	9	5	55
Total	124	63	51

With the approaching influenza season in the United States, the media are giving avian influenza enormous attention and, with the recent outbreak of SARS fresh in the public mind,<sup>19</sup> there is growing anxiety about avian influenza and what we can do as individuals to protect ourselves and our families. We offer the following suggestions to practicing physicians that may help in answering questions that patients are asking.

#### 1. WILL GETTING A FLU SHOT PROTECT ME FROM AVIAN INFLUENZA?

No, the annual flu shot will not provide any protection against the new avian H5N1 influenza strain that originated in Asia. However, the current endemic strains that predictably cause epidemic disease each winter kill 30,000 to 50,000 individuals in the United States each year, and getting the 2005-2006 flu shot remains as important this year as ever. This shot is especially important for the elderly, the immunocompromised, pregnant women, children, and all who come in contact with these high-risk groups, including other family members, household contacts, and health care workers. Being immunized greatly reduces elderly or otherwise vulnerable persons' risk of becoming so ill with flu caused by these strains that they have to be hospitalized or die.

#### 2. WHAT CAN I DO TO PROTECT MYSELF AGAINST INFLUENZA—ESPECIALLY IF I TRAVEL FREQUENTLY?

Travelers to countries where avian influenza is endemic in bird populations should avoid contact with poultry or contact with surfaces that may have been contaminated by poultry or their feces or secretions. This includes visits to poultry farms or visiting “wet markets” where live birds are sold or places where wild birds congregate in large numbers. Consumption of uncooked poultry or poultry products from these countries should also be avoided. Freezing and refrigeration do not substantially reduce the concentration or virulence of these viruses in meat; thus, it is essential to follow safe food-handling procedures (Table 2).

It must be emphasized that there is no evidence whatsoever that domestic poultry products purchased in North America pose any risk. However, all foods of avian ori-

TABLE 2. Avian Influenza and Safe Food-Handling Practices

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Separate raw meat from cooked or ready-to-eat foods. Do not use same chopping board or knife, do not place cooked meat back on same surface it was on before cooking
Do not use raw or soft-boiled eggs in food preparations that will not subsequently be cooked
Wash hands thoroughly with soap and water after handling frozen or thawed poultry. Wash or disinfect surfaces and utensils that have been in contact with raw poultry
Cook food thoroughly. Ensure that poultry meat reaches 70°C (158°F) or that the meat is no longer pink. Eggs should not be runny

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gin—eggs and poultry meat—must be cooked well, mainly to prevent infection caused by enteric bacteria such as *Salmonella* and *Campylobacter*. The avian influenza virus is rapidly killed by heat; hence, eating adequately cooked poultry products, even if they were contaminated by avian influenza virus, would not pose a health hazard.

These precautions may be especially important for persons who hunt and eat wild waterfowl. The evidence suggests that the H5N1 avian influenza virus is being spread beyond Asia by migratory water birds, especially ducks. It is likely that the Asian H5N1 strain will be detected in North American birds before long, having spread from Siberia on flyways through Alaska and Canada, and wild ducks or geese are likely to be the first North American birds to be infected.

Practicing consistent hand hygiene reduces the risk of transmission of most respiratory infections. This can be done by conventional hand washing with soap and water or by using alcohol-based, waterless hand sanitizers when hands are not visibly soiled. Hand sanitizers, especially in the convenient travel-size personal containers, are often a more practical option for the traveler.

At this time, the Centers for Disease Control and Prevention has not recommended that the general public avoid travel to any country affected by avian influenza. However, checking the Centers for Disease Control and Prevention travel Web site ([www.cdc.gov/travel](http://www.cdc.gov/travel)) for the most current information before a future trip is prudent.

### 3. DO ANTIVIRALS WORK? SHOULD I HAVE MY OWN SUPPLY OF ANTIVIRALS?

The H5N1 virus is resistant to the oldest class of antivirals effective against the influenza A virus, the adamantanes—amantadine and rimantadine. In contrast, the neuraminidase inhibitors—oseltamivir (Tamiflu) and zanamivir (Relenza)—have been shown to have good activity against most of the H5N1 strains.

Giving prescriptions for these drugs to individual patients in advance of a pandemic, with no justifiable immediate clinical indication, means that the limited supplies of

these medications may be diverted from persons who need them, especially elderly and other compromised persons with acute influenza, and will create an even greater shortage of these drugs. Widespread, inappropriate use of these drugs may also promote drug resistance. Many health care centers, including the Mayo Clinic in Rochester, Minn, have preemptively restricted prescribing of oseltamivir, limiting it to patients with clear indications for treatment of probable influenza or its prevention. The Infectious Diseases Society of America and the Society of Healthcare Epidemiologists of America recently issued a joint position statement urging very restricted use of this class of anti-influenza drugs, and many state health departments have followed suit. The manufacturer recently halted shipments of oseltamivir.

From a public health standpoint, it is extremely important that any suspected human cases of Asian H5N1 influenza be immediately reported to the local and state public health authorities, and self-treatment may delay or prevent such reporting.

For all these reasons, we do not recommend giving prescriptions for oseltamivir or alternative antivirals to travelers to countries with current avian influenza outbreaks.

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For the latest updates on avian influenza, see the following Web sites:

Centers for Disease Control and Prevention	<a href="http://www.cdc.gov/flu.avian">www.cdc.gov/flu.avian</a>
Centers for Disease Control and Prevention Travelers' Health	<a href="http://www.cdc.gov/travel">www.cdc.gov/travel</a>
World Health Organization	<a href="http://www.who.int/csr/disease/avian_influenza">www.who.int/csr/disease/avian_influenza</a>
New Scientist Bird Flu	<a href="http://www.newscientist.com/channel/health/bird-flu">www.newscientist.com/channel/health/bird-flu</a>

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