

850 patients, 585 had adenocarcinoma, and 46 had large-cell carcinoma.

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1. Sandler AB, Johnson DH, Brahmer J, et al. Retrospective study of clinical and radiographic risk factors associated with early onset, severe pulmonary hemorrhage in bevacizumab-treated patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2006;24:Suppl:381S. abstract.
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92-8.
3. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184-91.

Human H5N1 Influenza

TO THE EDITOR: As is consistent with previous studies of outbreaks of avian influenza A (H5N1) virus, the epidemiologic investigations reported by Kandun et al. in Indonesia and by Oner et al. in Turkey (Nov. 23 issue)^{1,2} show that H5N1 virus primarily infects young people (median age, 9 years). As of late November 2006, 258 cases of human H5N1 virus infection had been identified. More than half of the patients were under the age of 20 years (median age, 18.5 years), and 25% of them were under the age of 10 years. Although both studies report clusters within families and cite exposure to dead poultry as a common risk factor, it is unlikely that the intensity of exposure differed among household members. Rather, higher incidence rates in children may represent age-dependent differences in host susceptibility to H5N1 virus infection. Human infection is mediated by a receptor recognized by avian influenza (α 2,3-linked sialic acid) that is expressed in the lower respiratory tract.³ In children this receptor may be expressed in the upper airway, increasing the risk of infection. Indeed, α 2,3-linked sialic acids are homogeneously distributed in the human fetal lung, and the expression of the receptor appears to decrease with age.⁴

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1. Kandun IN, Wibisono H, Sedyaningih ER, et al. Three Indonesian clusters of H5N1 virus infection in 2005. *N Engl J Med* 2006;355:2186-94.
2. Oner AF, Bay A, Arslan S, et al. Avian influenza A (H5N1) infection in eastern Turkey in 2006. *N Engl J Med* 2006;355:2179-85.
3. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. Avian flu: influenza virus receptors in the human airway. *Nature* 2006;440:435-6.

4. Cerna A, Janega P, Martanovic P, Lisy M, Babal P. Changes in sialic acid expression in the lung during intrauterine development of the human fetus. *Acta Histochem* 2002;104:339-42.

TO THE EDITOR: Human H5N1 virus infection can be difficult to diagnose. In the report by Oner et al., the results of nasopharyngeal swabs were mostly negative. Positive results were obtained on polymerase-chain-reaction (PCR) assays of tracheal aspirates and lung-tissue samples. These results are predictable, since the receptors for the attachment of H5N1 virus are located predominantly around alveoli and terminal bronchioles and become progressively more rare toward the trachea.¹

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1. van Riel D, Munster VJ, de Wit E, et al. H5N1 virus attachment to lower respiratory tract. *Science* 2006;312:399.

TO THE EDITOR: The Perspective article by Webster and Govorkova¹ accompanying the reports by Kandun et al. and Oner et al. is perhaps the best available published summary of the emergence, evolution, and proliferation of H5N1 virus, an important emerging animal and human pathogen. Nonetheless, the time line that the authors provide does not include the four retrospectively confirmed cases of human H5N1 virus infection that occurred in Korea between December 2003 and March 2004 and another five confirmed cases that occurred in Japan during February and March 2004 among poultry workers and persons involved in the culling of infected poultry. The cases in

Japan were not reported until 10 months after they had been confirmed, and the cases in Korea were not confirmed until more than 2 years after they had occurred. The existence of these often overlooked nonfatal cases of human H5N1 virus infection illustrate the many impediments we face in refining our understanding of the epidemiology, risks, and potential effects of this disease in human populations.

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1. Webster RG, Govorkova EA. H5N1 influenza — continuing evolution and spread. *N Engl J Med* 2006;355:2174-7.

DR. ONER AND COLLEAGUES REPLY: That the expression of α 2,3-linked sialic acid receptor might be a reason for the high incidence of the disease in young patients is theoretical. To assess this concern, an understanding of the culture and traditions of the countries where avian influenza outbreaks have occurred is required. In the families of the patients in our study, exposure was more intensive in children than in their parents. People in this area of Turkey do not believe that the illness of chickens can be transmitted to humans. Therefore, the children played with the poultry, kissing and sleeping with them even when the birds were ill. However, the parents typically had contact with the chickens only while preparing them for cooking and eating them. We believe that contact with the secretions of the sick birds is an important risk factor and that children had more intensive contact with the poultry. Furthermore, if there were a relationship between viral-receptor intensity in young children and disease incidence, we would expect to see more cases in the first years of life, which has not been observed. Cerna et al.¹ have studied sialic acid expression in relation to developmental maturity of the lung and have shown that there is a slight decrease in sialic acid expression in the lungs before birth. Therefore, we think that children are affected by avian influenza viruses by the same mechanism that mediates adult infection.

We agree with Pawitan that human H5N1 virus infection is difficult to diagnose. Although the results of some nasopharyngeal swabs were negative in our study, all tracheal aspirates and lung-tissue samples were positive on real-time PCR assay. As Pawitan states, the receptors for the

attachment of avian influenza virus are located mostly around alveoli and terminal bronchioles.²

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1. Cerna A, Janega P, Martanovic P, Lisy M, Babal P. Changes in sialic acid expression in the lung during intrauterine development of the human fetus. *Acta Histochem* 2002;104:339-42.
2. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. Avian flu: influenza virus receptors in the human airway. *Nature* 2006;440:435-6.

DR. KANDUN AND COLLEAGUES REPLY: Most human cases of highly pathogenic H5N1 virus infection have been sporadic to date, but family clusters have occurred in several countries. Direct physical contact with sick or dead poultry has been identified as the primary risk factor.^{1,2} The reported intensity of exposure to diseased or dead poultry can vary substantially among family members in households of patients who have H5N1 virus infection. In our study, all three patients and the unaffected family members in cluster 3 were similarly exposed to diseased or dead poultry, as were many neighbors who never became ill. No patients or unaffected family members in clusters 1 and 2 had known contact with sick or dead poultry. In addition to exposure to H5N1 virus, susceptibility to human infection with H5N1 viruses could be mediated by age or immunologic, genetic, or other factors. The question of whether genetic or other factors, such as those affecting the expression of the host inflammatory response,³ might influence the severity of disease after H5N1 virus infection should also be investigated.

In our study, throat specimens had a higher yield for detecting H5N1 virus than did nasal specimens, and H5N1 viral RNA levels were higher in throat specimens than in nasal specimens in another study.³ For detection of H5N1 viral RNA by real-time PCR in patients with suspected H5N1 virus infection, specimens should be collected from different respiratory sites on multiple days, including nasal and throat swabs from patients who are not undergoing mechanical ventilation and endotracheal aspirates from intubated pa-

tients.⁴ Testing of nasal-swab specimens from patients with suspected H5N1 virus infection can also help detect human influenza A and B viruses that bind to α 2,6-linked sialic acid receptors located primarily in the upper respiratory tract.⁵

Two minor inaccuracies appear on page 2188 of our article. In Figure 1, the hospitalization date for Patient 2A should have been 9/6, rather than 9/3. On the same page, under the heading “Cluster 2,” line 3 of the second paragraph should have read, “Four days after his aunt was hospitalized, he had onset of fever,” rather than “three days.” We regret the errors.

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1. Areechokchai D, Jiraphongsa C, Laosiritaworn Y, Hanshaworakul W, O'Reilly M. Investigation of avian influenza (H5N1) outbreak in humans — Thailand, 2004. *MMWR Morb Mortal Wkly Rep* 2006;55:Suppl 1:3-6.

2. Pham DN, Hoang LT, Nguyen TKT, et al. Risk factors for human infection with avian influenza A H5N1, Vietnam, 2004. *Emerg Infect Dis* 2006;12:1841-7.

3. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006;12:1203-7.

4. World Health Organization. Collecting, preserving and shipping specimens for the diagnosis of avian influenza A(H5N1) virus infection. Guide for field operations. 2006 (Accessed March 8, 2007, at http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_EPR_ARO_2006_1/en/index.html.)

5. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y. Avian flu: influenza virus receptors in the human airway. *Nature* 2006;440:435-6.

DRS. WEBSTER AND GOVORKOVA REPLY: Dudley raises important unresolved issues about the timely detection and reporting of serologically confirmed cases of H5N1 infection in humans in South Korea and Japan between December 2003 and March 2004. Because of limited space, our Perspective article did not address the retrospective human cases of H5N1 in South Korea and Japan. The surprising finding is the low incidence of infection among humans after contact with infected poultry. The reemergence of H5N1 in poultry in both Vietnam and South Korea indicates that H5N1 virus continues to emerge and that the focus for eventual control may be domestic waterfowl.

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Fetal Pulse Oximetry and Cesarean Delivery

TO THE EDITOR: The study of fetal pulse oximetry and cesarean delivery reported by Bloom et al. (Nov. 23 issue)¹ perhaps gives us an interesting insight into clinicians' behavior. The authors claim that fetal oxygen monitoring does not alter the rate of cesarean delivery. However, the reason for the lack of differences in cesarean rates and infant outcomes between the “masked” and “open” groups may reflect the difficulty of the clinicians in interpreting the fetal oxygen saturation values and therefore in including this information in intrapartum management. In support of this suggestion, among the patients with reassuring fetal heart-rate tracings, 25.1% had low oxygen saturation. If the clinicians had been acting on their knowledge of the oxygen saturation levels, one would expect a higher rate of cesarean section in the open group than was reported. The fact that intrapartum management was left to the discre-

tion of the attending physician, without any clear guidelines on abnormalities in the level of fetal oxygen saturation and in the duration and frequency of low values, makes uncertain the authors' conclusion that the knowledge of fetal oxygen saturation may be of no benefit.

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1. Bloom SL, Spong CY, Thom E, et al. Fetal pulse oximetry and cesarean delivery. *N Engl J Med* 2006;355:2195-202.

THE AUTHORS REPLY: We differ with the assertion by Dr. Peek and colleagues that we failed to provide attending physicians with clear guidelines regarding an abnormal level of fetal oxygen satu-