Co-circulation of influenza A(H5N1) and seasonal influenza viruses among humans and animals could lead to co-infections, reassortment, and emergence of novel viruses with pandemic potential. We assessed the timing of subtype H5N1 outbreaks among poultry, human H5N1 cases, and human seasonal influenza in 8 countries that reported 97% of all human H5N1 cases and 90% of all poultry H5N1 outbreaks. In these countries, most outbreaks among poultry (7,001/11,331, 62%) and half of human cases (313/625, 50%) occurred during January–March. Human H5N1 cases occurred in 167 (45%) of 372 months during which outbreaks among poultry occurred, compared with 59 (10%) of 574 months that had no outbreaks among poultry. Human H5N1 cases also occurred in 59 (22%) of 267 months during seasonal influenza periods. To reduce risk for co-infection, surveillance and control of H5N1 should be enhanced during January–March, when H5N1 outbreaks typically occur and overlap with seasonal influenza virus circulation.

Humans are at risk for H5N1 infection if they have direct or close contact with infected domestic poultry, such as by handling sick animals or their byproducts, caregiving, slaughtering, and butchering; infection can also occur through some forms of indirect contact (e.g., proximity to live poultry or wet markets) (5,6). During 2003–2013, more than 645 human cases of HPAI H5N1 were confirmed; the case-fatality rate was ≈60% (7). H5N1 viruses have not yet acquired the ability to be transmitted between humans beyond 3 generations, therefore failing to show sustained human-to-human transmission (8). However, these viruses have wide geographic distribution and the potential to reassort with human seasonal influenza viruses. These characteristics mean that clarifying the timing of H5N1 outbreaks among poultry and infections in humans may be useful for prevention and control activities.

Recently published data suggest a seasonal pattern to H5N1 virus infection among domestic and wild birds (5,9–13). Park et al. noted that H5N1 outbreaks among poultry and infections in humans in Southeast Asia occurred in the cooler months during 1997–2006 (9). Other studies from Southeast Asia have suggested that decreasing temperatures may correlate with an increase in the number of H5N1 outbreaks among birds (14,15). Although ecologic studies suggest that H5N1 virus activity may occur during predictable times of the year, a systematic analysis of global poultry and human H5N1 data has not tested this hypothesis. In this study, we explored whether H5N1 outbreaks among domestic poultry and human H5N1 cases occurred in temporal proximity, occurred during certain climate conditions, or overlapped with human seasonal influenza epidemics.

Methods
Timing of H5N1 Outbreaks among Poultry
To describe the temporal patterns of H5N1 outbreaks among poultry worldwide, we extracted the number of monthly outbreaks reported by 52 countries as immediate notifications to the World Organisation for Animal Health (OIE) during January 2004–December 2013 (16). We used
the reported onset month as the occurrence month for each outbreak. Egypt and Indonesia stopped submitting immediate notifications of new H5N1 outbreaks among poultry after H5N1 in poultry was declared endemic: for Egypt in July 2008, and for Indonesia in September 2006. To obtain the number of monthly outbreaks for these countries, we extracted the number from their OIE biannual disease reports. If only the number of new cases but not the number of outbreaks in which they occurred was reported, we classified the month as having 1 outbreak.

For each country and year, we designated the peak month of H5N1 activity as the month that had the largest number of reported H5N1 outbreaks among poultry. Next, we identified the average peak month of H5N1 activity for each country (e.g., if the peak months in a hypothetical country occurred during January 2010, February 2011, and March 2012, then the average peak month during this period would have been February for this country).

### Timing of Human H5N1 Cases and Poultry H5N1 Outbreaks

We identified the monthly number of human H5N1 cases reported to the World Health Organization (WHO) during January 2004–June 2013. Initially, we obtained data from all 15 countries that reported human H5N1 cases since January 2004 (Figure 1). We then restricted the analysis to the 8 countries that reported 97% of all human H5N1 cases and that reported recurrent H5N1 activity among humans and poultry. To examine the temporal relationship between human H5N1 cases and H5N1 outbreaks among poultry, we compared the number of human H5N1 cases to the number of poultry H5N1 outbreaks for each month from these 8 countries (7,17). We then analyzed the association of the monthly number of human H5N1 cases and poultry H5N1 outbreaks by using the Spearman coefficient (p).

### Timing of Human Seasonal Influenza and H5N1 Cases

To clarify the hypothetical risk for human co-infection with avian and seasonal influenza viruses, we investigated the extent to which human H5N1 cases occurred during months when seasonal influenza viruses were circulating. To determine whether H5N1 and seasonal influenza viruses were identified among humans during the same months, we obtained seasonal influenza surveillance data collected by WHO during 2004–2013 (18). We estimated periods of seasonal influenza epidemics by assessing the months during which the proportion of respiratory samples that tested positive for influenza viruses was higher than the annual mean (19). We then identified the number of months during which human H5N1 cases and human seasonal influenza epidemics occurred during the same month.

### Ambient Temperature, Human H5N1 Cases, and Poultry H5N1 Outbreaks

To determine whether cool ambient temperature was associated with the number of poultry H5N1 outbreaks, we...
Results

Timing of Poultry H5N1 Outbreaks

During January 2004–June 2013, a total of 12,610 poultry H5N1 outbreaks in 52 countries were reported to the OIE. Fifteen of these countries also reported laboratory-confirmed H5N1 cases in humans to WHO. Of these 15 countries, 8 (Bangladesh, Cambodia, China, Egypt, Indonesia, Thailand, Turkey, and Vietnam) accounted for 11,331 (90%) of worldwide poultry H5N1 outbreaks. These 8 countries served as the basis for our analyses. Four of the 8 countries (Bangladesh, China, Egypt, and Turkey) are classified as Northern Temperate or Subtropical countries because most of their land mass is north of the Tropic of Cancer (latitude 23.27°N). The other 4 countries (Cambodia, Indonesia, Thailand, and Vietnam) are classified as tropical because they are located between the Tropics of Cancer and Capricorn (Table).

The 8 countries provided a total of 79 whole years (948 months) of data on outbreaks among poultry; 2013 data from Indonesia were not complete and therefore were not included in the analysis. Outbreaks were reported during 39% (365/948) of the study months. Most poultry H5N1 outbreaks (8,616/11,331, 76%) were reported during January–March. February had the highest total number of reported poultry H5N1 outbreaks, 3,118. Figure 2 provides the cumulative number of poultry H5N1 outbreaks reported each month by country and illustrates how these outbreaks clustered during January–March.

Poultry H5N1 Outbreaks and Human H5N1 Cases

During 2004–2013, the 8 study countries reported nearly all (625/645, 97%) human H5N1 cases (Table); cases were reported in 227 (24%) of the 948 study months. As seen with H5N1 outbreaks among poultry, half of human cases (313/625, 50%) occurred during January–March, and January had the highest number of reported H5N1 cases among humans (p = 0.8, p = 0.004) (Figures 2, 3). At least 1 human case of H5N1 infection occurred during 168 (45%) of the 374 months in which ≥1 outbreak in poultry occurred, compared with 59 (10%) of 574 months without outbreaks among poultry (relative risk = 5, p<0.001). After their initial identification, poultry H5N1 outbreaks and human H5N1 cases recurred concurrently during October–March in 24 (34%) of 70 study year equivalents.

Human H5N1 and Seasonal Influenza Activity

Seasonal influenza was epidemic in 267 (30%) of 888 months for which data were available. Human H5N1 cases occurred in 59 (22%) of these 267 months (Figure 4).

H5N1 Outbreaks in Poultry during Colder Temperatures

In each of the 8 countries, the number of poultry H5N1 outbreaks was highest during months with the lowest average ambient air temperature (Figure 2). In our regression model, colder ambient temperature was also ecologically associated with an increase in the number of poultry H5N1 outbreaks and human cases. For each decrease in temperature by 3.3°C, 1 additional poultry H5N1 outbreak was reported (p = 0.004), and for each decrease in temperature by 0.3°C, 1 additional H5N1 human case was reported (p<0.001). Precipitation was co-linear to temperature, however, and was dropped from the analysis.

Discussion

Our study reaffirms that, in Southeast Asia, H5N1 outbreaks among poultry and human H5N1 cases often

Abstracted monthly mean temperature data for each country from the US National Oceanic and Atmospheric Administration or from the Vietnam General Statistics Office (20,21). We used linear regression models to determine whether the monthly number of poultry H5N1 outbreaks and number of human H5N1 cases were negatively associated with mean monthly temperature and precipitation (e.g., after accounting for the absolute value of each country’s central latitude [19] and 2-way interactions) (22).

Discussion

Our study reaffirms that, in Southeast Asia, H5N1 outbreaks among poultry and human H5N1 cases often
occur seasonally, during months when temperatures are relatively cool. Even when accounting for H5N1-endemic countries outside Southeast Asia, most (>50%) poultry H5N1 outbreaks and human H5N1 cases of H5N1 infection occurred during January–March. Human and animal health officials in affected countries should consider exploring the value of enhanced surveillance, flock biosecurity, and live bird market disinfection and/or rest days during periods when H5N1 viruses are typically detected (22–24).

Our analysis of 2004–2013 data from 8 countries also suggests that lower ambient temperatures are associated with H5N1 outbreaks among poultry, even though half of our data came from tropical countries, where annual temperature variations are often small. These results are similar to those described by Park and Glass, who observed poultry H5N1 outbreaks during 1997–2006 in Southeast Asia and China and concluded that these outbreaks most often occurred during colder months (10). Other studies have found similar associations (5,25,26). A decrease in temperature can

Figure 2. Outbreaks of highly pathogenic avian influenza A(H5N1) infection by month (white bars) and mean temperature (black lines) for the 8 countries that reported 90% of worldwide poultry H5N1 outbreaks during 2004–2013. Stars indicate month with highest average number of outbreaks for each country. Temperature data were not available for Cambodia.
Our findings support and demonstrate the feasibility of integrating human and animal surveillance for avian influenza and other zoonotic diseases. Combining the expertise from multiple surveillance systems can increase the detection rate of H5N1 cases in humans from 57% to 93% and of epizootics from 40% to 53% (36). This recommendation for an integrated H5N1 surveillance approach enables better prediction of disease risk and identification of outbreaks (37). Such approaches can assist in filling in gaps in human and animal surveillance systems (36, 37).

This study has several limitations. H5N1-endemic countries are not required to report immediate notifications. H5N1 reports also often are limited because of a lack of resources for surveillance, laboratory capacity to confirm H5N1, and, often, the political will to report outbreaks in poultry that may result in substantial economic losses (38). No formal case definition for a poultry H5N1 outbreak has been developed. During our study period, surveillance practices for human and poultry H5N1 and human seasonal influenza were not standardized; in fact, outbreaks among poultry might be more likely to be reported during periods when human H5N1 cases occurred. Further standardization of surveillance and reporting of influenza outbreaks in humans and animals might help clarify the epidemiology of these viruses (19).

Health authorities in H5N1 virus–affected countries should consider enhanced surveillance for H5N1 viruses among domestic poultry and humans in anticipation of increased H5N1 activity among poultry (22–24). These lessons may also be relevant to the management of avian influenza A(H7N9) virus outbreaks in China, which have occurred during similar times of the year.

**Acknowledgments**

We thank James Kile, Kathy Sturm-Ramírez, and Makhdim Ahmed for providing temperature data from sites not represented in National Oceanic and Atmospheric Administration datasets.

Dr. Durand is an Epidemic Intelligence Service Officer with the Influenza Division of the US Centers for Disease Control and Prevention. Her research interests include influenza and other infectious diseases.
Timing of Influenza Worldwide, 2004–2013

Figure 4. Human cases of highly pathogenic avian influenza A(H5N1) infection and seasonal influenza rates for 8 study countries, by month. Bars indicate the proportion of human respiratory samples that tested positive for seasonal influenza viruses; black bars indicate months during which seasonal influenza was epidemic and a human H5N1 case was reported. Years covered for each country are provided along x-axes.

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Address for correspondence: Eduardo Aziz-Baumgartner, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop A32, Atlanta, GA 30329-4027, USA; email: ea@cdc.gov

Biomarker Correlates of Survival in Pediatric Patients with Ebola Virus Disease

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