main diagnostic methods used were bacterial culture (46%) and PCR (45%). However, 12% of respondents indicated that they had changed the type of diagnostic test they used beginning in 2012; among these respondents, 33% were more likely to use pertussis culture and 63% were more likely to use PCR or to use culture and PCR. Of total respondents, 22% indicated that they ordered diagnostic tests more frequently since the beginning of 2012.

Our investigation has limitations. We could not determine a survey response rate because of extensive overlap of the email lists used, and we lacked access to the lists; the response rate is assumed to be very low. Respondents included in the analysis may not have been representative of the broader NYC provider community. In addition, respondents may not have uniformly interpreted the survey because of the subjective nature of some survey questions, and recall bias may have affected responses. Also, respondent awareness of the outbreak is likely overestimated because the email lists used for survey distribution were used during the outbreak to distribute health alerts. Despite these limitations, our investigation shows the value of Web-based surveys distributed by email to gather information rapidly from a large provider community in a cost-effective and practical manner.

This investigation indicates the importance of provider knowledge and practices for public health surveillance data. High awareness of an outbreak, increased clinical suspicion of pertussis, and increased frequency of diagnostic testing likely contributed to a sustained elevation in pertussis incidence. Advisory alerts and media reports were successful mechanisms for disseminating information to providers during the outbreak and likely altered provider behaviors that contributed to the increase in reported pertussis incidence. Previous reports have documented increased submission of disease notifications after media coverage of health concerns (*4,5*). Responses to our survey also highlight how pertussis incidence may be routinely underestimated because providers do not suspect the disease or test for it consistently.

This work was supported in part by an appointment to the Applied Epidemiology Fellowship Program administered by the Council of State and Territorial Epidemiologists and funded by the Centers for Disease Control and Prevention (Cooperative Agreement 5U38HM000414-5).

References

1. Davis SF, Strebel PM, Cochi SL, Zell ER, Hadler SC. Pertussis surveillance—United States, 1989–1991. MMWR CDC Surveill Summ. 1992;41:11–9.
2. Centers for Disease Control and Prevention. Pertussis cases by year (1922–2014). 2015 Mar 6 [cited 2015 Sep 8]. http://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html
3. Centers for Disease Control and Prevention. 2013 Final pertussis surveillance report. 2014 Oct [cited 2015 Sep 8]. http://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2013.pdf
4. Olowokure B, Clark L, Elliot AJ, Harding D, Fleming A. Mumps and the media: changes in the reporting of mumps in response to newspaper coverage. J Epidemiol Community Health. 2007;61:385–8. http://dx.doi.org/10.1136/jech.2005.042598
5. Davis JP, Vergeront JM. The effect of publicity on the reporting of toxic-shock syndrome in Wisconsin. J Infect Dis. 1982;145:449–57. http://dx.doi.org/10.1093/infdis/145.4.449

Address for correspondence: Robert J. Arciuolo, New York City Department of Health and Mental Hygiene, 42-09 28th St, CN #21, Long Island City, NY 11101, USA; email: rarciuolo@health.nyc.gov

Hemophagocytic Lymphohistiocytosis and Progressive Disseminated Histoplasmosis

Kenice Ferguson-Paul, Spencer Mangum, Ashley Porter, Vasiliki Leventaki, Patrick Campbell, Joshua Wolf

Author affiliations: St. Jude Children's Research Hospital, Memphis, Tennessee, USA (K. Ferguson-Paul, S. Mangum, A. Porter, V. Leventaki, P. Campbell, J. Wolf); University of Tennessee Health Sciences Center, Memphis (K. Ferguson-Paul, S. Mangum, A. Porter, J. Wolf)

DOI: http://dx.doi.org/10.3201/eid2206.151682

To the Editor: Progressive disseminated histoplasmosis (PDH) of infancy occurs most commonly in previously healthy infants <1 year of age, typically after exposure to a large fungal inoculum (*1*). Even with treatment, the disease is fatal in ≈13% of cases (*1*). Common symptoms include fever, hepatosplenomegaly, lymphadenopathy, and failure to thrive. Laboratory abnormalities frequently include cytopenia and coagulopathy (*1*,*2*). Many clinical manifestations of PDH overlap with those of the hyperinflammatory condition hemophagocytic lymphohistiocytosis (HLH), and co-existence of HLH and histoplasmosis has been reported in adults. We report a case of simultaneous PDH and HLH in an infant.

A 6-month-old African American girl was brought for treatment to St. Jude Children's Research Hospital in April 2015 with a 1-month history of daily fever. Her history was notable only for a methicillin-resistant *Staphylococcus aureus* skin abscess diagnosed when she was 5 months old; it was drained, and she received oral clindamycin.

On initial evaluation, she had fever, lethargy, and hepatosplenomegaly. Laboratory testing showed pancytopenia and mild hepatitis, and abdominal ultrasound confirmed hepatosplenomegaly. After admission, respiratory distress

developed due to worsening hepatosplenomegaly. Additional laboratory testing revealed elevated ferritin (1,218 ng/mL; reference 10–100 ng/mL), low fibrinogen level (78 mg/dL; reference 185–443 mg/dL), elevated triglycerides (378 mg/dL; reference 0–149 mg/dL) and elevated soluble interleukin-2 receptor (21,530 pg/mL; reference <1,033 pg/mL). An HIV serologic test result was negative. Histologic examination of bone marrow showed many activated macrophages, including some with hemophagocytosis (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/22/6/15-1682-Techapp1.pdf). On the basis of clinical and laboratory findings, the patient received a diagnosis of HLH, and treatment was initiated with etoposide and dexamethasone.

Further evaluation of the bone marrow sample demonstrated fungal elements characteristic of *Histoplasma capsulatum* (online Technical Appendix). *Histoplasma* antigen assays on serum and urine samples were positive for *H. capsulatum* above the limit of quantification. *Histoplasma* complement-fixation antibody titers for both yeast and mycelial antigens were negative, but immunodiffusion antibody tests for H and M bands were positive. Cerebrospinal fluid was also positive for *Histoplasma* antigen. Results of magnetic resonance imaging of the patient's brain were normal for age.

Because the patient's condition met diagnostic criteria for both HLH and PDH, she was given etoposide, dexamethasone, and liposomal amphotericin B (LAmB), according to treatment guidelines for both conditions (*3*,*4*). Supportive care included transfusion of packed red blood cells, platelets, cryoprecipitate, and fresh frozen plasma. Her fever resolved after 10 days, and other symptoms resolved after 2 weeks. After 16 days of hospitalization, she was discharged to complete a 6-week course of LAmB with a plan to transition to oral itraconazole and complete 1 year of therapy, according to guidelines of the Infectious Diseases Society of America (*4*).

HLH is a rare disease, characterized by impaired function of natural killer and cytotoxic T-lymphocytes that results in an unchecked inflammatory response. If not treated promptly, HLH can progress rapidly to multiorgan failure and death (*3*). HLH is categorized into familial or secondary forms. Familial HLH is caused by mutations in ≥1 of the genes required for perforin-dependent lymphocyte cytotoxicity; secondary HLH occurs in a person who does not have genetic risk factors (*3*). Both forms can be triggered by infection or malignancy (*3*).

Diagnosis of HLH is based on clinical assessment (Table); no definitive diagnostic test exists (*6*). Initial treatment of HLH involves the use of corticosteroids, etoposide, or other drugs to block the hyperinflammatory response and specific therapy for the inciting infection if available (*7*). In some cases, in which a treatable inciting infection is identified, antimicrobial drug therapy alone might be sufficient. However, concurrent immunosuppressive therapy is usually recommended, especially for patients who are critically ill or whose condition is clinically deteriorating (*3*).

Table. Diagnostic criteria for HLH*

Criterion	HLH reference	Patient in this report
Fever	≥38.5°C	40°C†
Splenomegaly	Present	Present†
Cytopenia, 2 of 3 lineages		
ANC, cells/mm^3	<1,000	1,500
Hemoglobin, g/dL	<9	5.9†
Platelet count, × 10^3/μL	<100	11†
Low fibrinogen, mg/dL	<150	78†
or		
High triglycerides, mg/dL	>265 fasting	378†
Hemophagocytosis	Present	Present†
NK cell activity	Low or absent	Normal
Elevated ferritin, ng/mL	>500	317 (max 1,218)†
Soluble IL-2 receptor, pg/mL	>2,400	21,530†

*ANC, absolute neutrophil count; HLH, hemophagocytic lymphohistiocytosis; IL-2, interleukin-2; NK, natural killer.
†Criteria met by this patient. The HLH-2004 diagnostic criteria require either a molecular/genetic diagnosis consistent with HLH or fulfillment of 5 of the 8 criteria shown. Adapted from (*5*).

Many clinical manifestations of disseminated histoplasmosis, including prolonged fever, hepatosplenomegaly, pancytopenia, and coagulopathy, overlap with those of HLH. Because of the similarity in manifestations, differentiating these 2 conditions is challenging without specialized testing. Furthermore, laboratory tests specific for HLH, such as measuring soluble interleukin-2 receptor, have not been investigated in patients with isolated PDH, so whether they distinguish between the 2 conditions is unclear. To add further complexity, coexisting histoplasmosis and HLH has been described in several adult patients (*5, 8–10*). However, whether HLH identification and adjunctive immunosuppressive therapy leads to improved outcomes in this situation is unknown.

On the basis of our investigation of this infant with HLH and PDH, we recommend that all infants exhibiting HLH in *Histoplasma*-endemic regions be assessed for histoplasmosis. In addition, the similarity with the clinical features of PDH and the difficulty in diagnosis of HLH without specialized testing raise the question of whether a large number of infants with PDH would also meet the diagnostic criteria for HLH. If so, currently poor outcomes of PDH might be related to co-existing HLH with failure to control the inflammatory response, and the outcomes could be improved by diagnosis and simultaneous treatment of both conditions. Further research is needed to investigate this phenomenon.

References

1. Odio CM, Navarrete M, Carrillo JM, Mora L, Carranza A. Disseminated histoplasmosis in infants. Pediatr Infect Dis J. 1999;18:1065–8. http://dx.doi.org/10.1097/00006454-199912000-00007
2. Quilter LA, Kleiman MB, Kirsch E, Wheat LJ. Disseminated histoplasmosis of infancy in one of the twins. Pediatr Infect Dis J. 2012;31:990–1. http://dx.doi.org/10.1097/INF.0b013e31825d31f7

3. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118:4041–52. http://dx.doi.org/10.1182/blood-2011-03-278127
4. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807–25. http://dx.doi.org/10.1086/521259
5. Townsend JL, Shanbhag S, Hancock J, Bowman K, Nijhawan AE. Histoplasmosis-induced hemophagocytic syndrome: a case series and review of the literature. Open Forum Infect Dis. 2015;2:ofv055. PMID: 26380347
6. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124–31. http://dx.doi.org/10.1002/pbc.21039
7. Trottestam H, Horne A, Arico M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood. 2011;118:4577–84. http://dx.doi.org/10.1182/blood-2011-06-356261
8. Majluf-Cruz AS, Hurtado Monroy R, Souto-Meirino C, del Rio Chiriboga C, Simon J. Hemophagocytic syndrome associated with histoplasmosis in the acquired immunodeficiency syndrome: description of 3 cases and review of the literature [in Spanish]. Sangre (Barc). 1993;38:51–5.
9. Keller FG, Kurtzberg J. Disseminated histoplasmosis: a cause of infection-associated hemophagocytic syndrome. Am J Pediatr Hematol Oncol. 1994;16:368–71.
10. Sanchez A, Celaya AK, Victorio A. Histoplasmosis-associated hemophagocytic syndrome: a case report. AIDS Read. 2007; 17:496–9.

Address for correspondence: Joshua Wolf, St. Jude Children's Research Hospital, Department of Infectious Diseases, 262 Danny Thomas Pl, Memphis, TN 38105, USA; email: joshua.wolf@stjude.org

Novel Avian Influenza A(H5N8) Viruses in Migratory Birds, China, 2013–2014

Li-Chen Zhou,[1] Jing Liu,[1] En-Le Pei,[1] Wen-Jie Xue,[1] Jia-Min Lyu, Yin-Ting Cai, Di Wu, Wei Wu, Yu-Yi Liu, Hui-Yu Jin, Yu-Wei Gao, Zheng-Huan Wang, Tian-Hou Wang

Author affiliations: Laboratory of Wildlife Epidemic Diseases, Shanghai Key Laboratory for Urban Ecological Processes and Eco-Restoration, School of Life Sciences, East China Normal University, Shanghai, China (L.-C. Zhou, J. Liu, J.-M. Lyu, Z.-H. Wang, T.-H. Wang); Shanghai Municipal Agency of Wildlife Conservation, Shanghai (E.-L. Pei, D. Wu, H.-Y. Jin); Chongming Dongtan National Nature Reserve, Shanghai (W.-J. Xue, W. Wu); Jiuduansha Wetland National Nature Reserve, Shanghai, China (Y.-T. Cai) Wildlife Conservation Section, Shanghai Municipal Forestry Bureau, Shanghai (Y.-Y. Liu); Research Center of Wildlife Disease, Key Laboratory of Jilin Province for Zoonosis Prevention and Control, Military Veterinary Research Institute of Academy of Military Medical Sciences, Changchun, China (Y.-W. Gao)

DOI: http://dx.doi.org/10.3201/eid2206.151754

To the Editor: Novel highly pathogenic avian influenza (HPAI) A(H5N8) virus infections were first detected in poultry in eastern China in 2010 (*1*); the virus caused outbreaks in South Korea and Japan in 2014 (*2*) and reached Europe and North America by early 2015 (*3–6*). Phylogenetic analysis indicated that novel HPAI subtype H5N8 viruses might have originated in China and then circulated in East Asia countries and that the global geographic dissemination of this virus was strongly associated with the migration of wild birds (*7*). However, the role of migratory birds in the initial introduction and spread of novel H5N8 strains in China and other countries in the region is unclear. Shanghai, located at the Yangtze River estuary on the eastern coast of China, is a crucial stopover for migratory birds in East Asia. We report the presence of novel H5N8 strains from migratory birds sampled in Shanghai from October 2013 through December 2014.

A total of 26 novel H5N8 viruses were detected from migratory ducks and curlews captured and swabbed during their wintering period at the coastal wetlands of Shanghai. We collected 19 H5N8 viruses from 16 common teals (*Anas crecca*), 2 falcated ducks (*A. falcata*), and 1 spot-billed duck (*A. poecilorhyncha*) sampled in 2013 and 7 viruses from Eurasian curlews (*Numenius arquata*) sampled in 2014. Common teals were also found to be infected with subtype H5N1, detected by N1 gene fragments in 3 mixed-infection and 2 single-infection samples (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/22/6/15-1754-Techapp1.pdf). Sequences from this study were deposited in GenBank (accession nos. KT936635–KT936716).

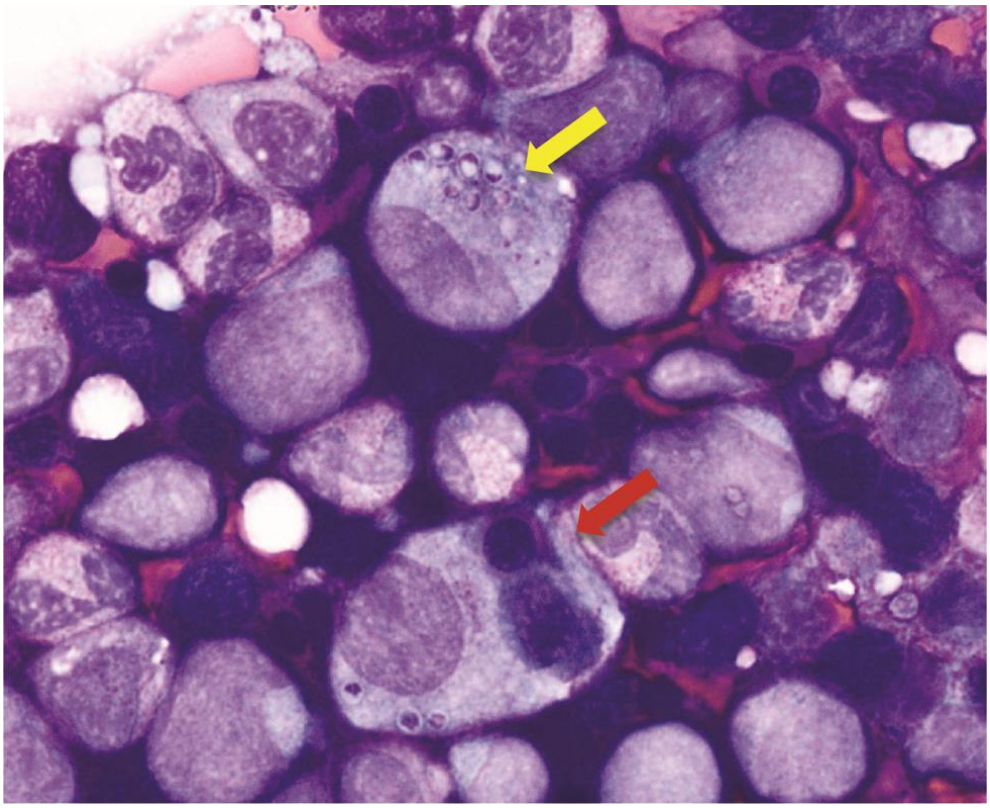
Homology BLAST (http://blast.st-va.ncbi.nlm.nih.gov/Blast.cgi) searches showed that H5 and N8 genes of 18 influenza A(H5N8) viruses in ducks had ≥98% similarity to H5N8 isolates W24 and 6D18 detected in poultry in Zhejiang Province (*2*), adjacent to Shanghai. The H5 gene in A/common teal/Shanghai/1108–1/2013(mixed) (PD1108-1) was 96% related to low pathogenicity avian influenza (LPAI) subtype H5N1 isolated from a European teal sampled in Russia in 2011 (GenBank accession no. KF462362). Of the 7 viruses from curlews, H5 and N8 isolates were closely related to isolates H68 and H297 from wild ducks reported in South Korea in early 2014 (*8*). Matrix genes of all novel subtype H5N8 viruses were closely related (95%–99%) to isolates from China (S11090, W24), Japan (156), and South Korea (Gochang1, S005) (online Technical Appendix Table).

[1]These authors contributed equally to this article.

Article DOI: http://dx.doi.org/10.3201/eid2206.151682

Hemophagocytic Lymphohistiocytosis and Progressive Disseminated Histoplasmosis

Technical Appendix



Technical Appendix Figure. Wright-Giemsa stain of the bone marrow biopsy specimen of a 6-month-old girl with hemophagocytic lymphohistiocytosis and progressive disseminated histoplasmosis. Imprints show cytoplasm-rich (activated) macrophages with hemophagocytosis (black arrow) and intracellular organisms (white arrow). Original magnification ×100. A color version of this figure is available online (http://wwwnc.cdc.gov/EID/article/22/6/15-1682-F1.htm).