Update: Pulmonary Hemorrhage/Hemosiderosis Among Infants—Cleveland, Ohio, 1993-1996

MMWR. 2000;49:180-184

A review within CDC and by outside experts of an investigation of acute pulmonary hemorrhage/hemosiderosis in infants has identified shortcomings in the implementation and reporting of the investigation described in MMWR1,2 and detailed in other scientific publications authored, in part, by CDC personnel.3-5 The reviews led CDC to conclude that a possible association between acute pulmonary hemorrhage/hemosiderosis and exposure to molds, specifically *Stachybotrys chartarum* by its synonym *S. atra*, was not proven. This report describes the specific findings of these internal and external reviews.

Background

In December 1994 and January 1997, articles in MMWR described a cluster of 10 infants from Cleveland, Ohio, with acute idiopathic pulmonary hemorrhage, also referred to as pulmonary hemosiderosis.1,2 The children resided in seven contiguous postal tracts and had had one or more hemorrhagic episodes, resulting in one death, during January 1993-December 1994. Preliminary results of a CDC case-control study2 indicated that hemorrhage was associated with (1) major household water damage during the 6 months before illness and (2) increased levels of measurable household fungi, including the toxin-producing mold *S chartarum* (synonym *S atra*).

These findings and the observation that trichothecene mycotoxins were produced in the laboratory by some *S chartarum* isolates recovered from the homes of study subjects have been published and referenced in peer-reviewed scientific literature.3,4 The hypothesis from the findings of the investigation was that infant pulmonary hemorrhage may be caused by exposure to potent mycotoxins produced by *S chartarum* or other fungi growing in moist household environments.3,5 The findings also were cited in environmental health guidelines,10,11 congressional testimony,12 and the popular media,13-16 and have been debated among industrial hygienists and other occupational and environmental health scientists.17-21 Despite caution that “further research is needed to determine . . . causality,”14 the findings have influenced closure of public buildings, cleanup and remediation, and litigation.10,22-28

In June 1997, a CDC scientific task force, in a review of the agency’s response to the problem, advised the CDC director that concerns about the role of *S chartarum* in pulmonary hemorrhage needed to be addressed. In response, CDC convened a multidisciplinary internal group of senior scientists (working group) and sought the individual opinions of outside experts. The working group and the outside experts conducted separate reviews of the Cleveland investigation. The working group reviewed background literature, internal CDC documents, and published CDC reports; examined the data set; and interviewed the principal investigators. The external experts reviewed relevant literature, including internal CDC documents and the working group report, and invited additional consultants to address specific topics. The working group and the external consultants each concluded that further work is needed to better describe the clinical problem, its public health impact, and the factors that put infants at risk.29-30

**Case Identification**

The reviewers had concerns about the characterization of the clinical problem as “hemosiderosis.” The acute presentation in all 10 cases, the narrow age distribution (6 weeks to 6 months), and the absence of iron deficiency suggest that the illness described in the cluster of cases in Cleveland4,5 is clinically distinct from idiopathic pulmonary hemosiderosis (IPH), the condition to which this cluster was linked.33 Hemosiderosis (ie, hemosiderin-laden macrophages in the interstitium and alveolar spaces of the lung) is a pathologic finding indicative of pulmonary bleeding of any type, not a unique characteristic of a specific disease, etiology, or pathophysiologic process.32,33 Therefore, in referring to the cluster of cases in Cleveland, the working group defined that cluster as acute idiopathic pulmonary hemosiderosis (AIPH) in infants. From the limited clinical and historic information available to the reviewers on cases added to the Cleveland series since the original cluster (D. Dearborn, Case Western Reserve Department of Pediatrics, personal communication, September 1999), the external consultants concluded that some of these additional cases,6 including several identified in a retrospective review of sudden infant death syndrome cases,7 do not conform to the clinical patterns of cases in the original cluster. Both groups of reviewers recognized limitations that precluded drawing conclusions about clinical or etiologic ties to IPH.

**Association of AIPH With Household Water Damage and Fungi**

Both groups of reviewers concluded that the available evidence does not substantiate the reported epidemiologic associations—between household water damage and AIPH6 or between household fungi and AIPH7—or any inferences regarding causality. The

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interpretation of water damage and its association with AIPH was considered to have been hampered by the limited descriptive information, by the lack of standard criteria for water damage, and by the absence of a standard protocol for inspecting and recording information from home to home. Similarly, assessment of exposure to fungi or mycotoxin was difficult to interpret because the methods did not distinguish between contamination and clinically meaningful exposure. No isolates or serologic evidence of exposure to fungi or mycotoxin were obtained in individual case-infants.

Evaluation of Analysis Methods

Three factors, considered together, contributed to the groups’ conclusions that S chartarum was not clearly associated with AIPH:

1. The working group found that the reported odds ratio (OR) of 9.8 for a change of 10 colony-forming units (CFU) per m³ was statistically unstable and potentially inflated. The estimated very sensitive to at least three influential steps or strategies in the analysis. First, the mean airborne S chartarum concentrations (CFU/m³) for each household were calculated incorrectly. Substituting the corrected means reduced the OR by 44% to 5.5. Second, the mean S chartarum value (CFU/m³) was imputed in one case home. The sample was collected many months after sampling in the other case homes and, along with all other household samples collected at the same time, produced unusually heavy growth of non-Stachybotrys fungi, suggesting important differences in sampling technique, laboratory procedure, or environmental conditions at the time of the sampling. Exclusion of this household from the analysis and correcting the means reduced the OR to 1.9. Third, pairing on age in a small data set created an unstable OR. Subject age was not expected to influence concurrent measurements of airborne fungi and did not correlate with the mean S chartarum CFU/m³. Therefore, the strategy to match cases and controls based on age was unnecessary and potentially misleading. Analysis without the matching variable reduced the OR from 9.8 to 1.5.

2. Although the methods specified that sampling be done in a blinded manner, one investigator correctly inferred the identity of many case homes and wanted to be certain to identify culturable fungi in these homes if they were present. As a result, the investigator collected twice the number of air samples from case homes as were collected from control homes. In addition, investigators used aggressive, nonstandardized methods to generate artificial aerosols for sampling (e.g., vacuuming carpets and pounding on furnace ducts and furniture), increasing the potential for differential exposure assessments of cases and controls if sampling were conducted in an unblinded manner.

3. Among homes classified as water damaged, the presence of any culturable airborne S chartarum was identified in similar percentages of case and control homes (four of eight compared with three of seven) (CDC, unpublished data, February 1997). Although the numbers were small, this provided little evidence of a difference in the presence of airborne S chartarum between water-damaged case and control homes. If the classifications of water damage were correct, this would suggest that water damage, or an unrecognized correlate of water damage, may be confounding any perceived association with S chartarum.

Overall, the reviewers concluded that on the basis of these limitations the evidence from these studies was not of sufficient quality to support an association between S chartarum and AIPH. In addition, the reviewers noted that evidence from other sources supporting a causal role of S chartarum in AIPH is limited. First, AIPH is not consistent with historic accounts of animal and human illness caused by S chartarum or related toxigenic fungi. Second, clusters of AIPH have not been reported in other flood-prone areas where growth of S chartarum or other toxigenic fungi might be favored. Third, the mold-disease association observed in the Cleveland investigation was not observed in the investigation of a similar Chicago cluster (34, CDC, unpublished data, May 1997).

Reported by: Office of the Director, CDC.

CDC Editorial Note: On the basis of the findings and conclusions in the reports of the CDC internal working group and the individual opinions of the external consultants, CDC advises that conclusions regarding the possible association between cases of pulmonary hemorrhage/hemosiderosis in infants in Cleveland and household water damage or exposure to S chartarum are not substantiated adequately by the scientific evidence produced in the CDC investigation. Serious shortcomings in the collection, analysis, and reporting of data resulted in inflated measures of association and restricted interpretation of the reports. The associations should be considered not proven; the etiology of AIPH is unresolved.

As a result of the reviews, CDC will implement the following:

1. CDC will continue to investigate cases of AIPH in infants, particularly when clusters of cases can be identified.
2. CDC will continue to consider possible associations between AIPH and many possible etiologies, including household water damage or exposure to environmental hydrophilic fungi/molds such as S chartarum. Standardized protocols will be recommended for data collection and environmental assessment.
3. CDC will assist in implementation of surveillance for individual cases or clusters of cases of AIPH in infants.
4. In collaboration with pediatric pulmonary specialists and with state and local health officials, a consistent standard surveillance case definition will be developed for reporting.
5. As part of future CDC investigations, CDC will enhance sampling and laboratory analytic methods to improve assessment of environmental exposures to molds/fungi.

Copies of the report of the working group and a synthesis prepared by CDC of the reports individually submitted by the external experts can be accessed at...
http://www.cdc.gov/od/ads, then click on “Pulmonary Hemorrhage/Hemosiderosis Among Infants.”

REFERENCES

13. See the first report described eight infants identified through November 1994. Two additional infants, identified in December 1994, were added to the original study.
14. An imputed value, 4 CFU/m³ (half the limit of detection divided by the number of plates), was used because colonies were observed on one or more of the plates, but were too few to count on the final plating and, therefore, recorded in the laboratory record as 0 CFU/m³.
15. The working group’s reported reanalysis used the value originally coded in the laboratory record (0 CFU/m³). The result was identical to that obtained by excluding the household from the analysis.

Imported Dengue—United States, 1997 and 1998

MMWR. 2000;49:248-253

1 table omitted.

Dengue is a mosquito-transmitted acute viral disease caused by one of four dengue virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Dengue is endemic in most tropical areas of the world and has occurred in U.S. residents returning from travel to such areas. CDC maintains a laboratory-based passive surveillance system for imported dengue among U.S. residents. The system relies principally on reports by clinicians to state health departments, which forward patient specimens to CDC for diagnostic testing. This report summarizes information about imported dengue cases among U.S. residents for 1997 and 1998, which indicates that most persons with a known travel history probably acquired infection in the Caribbean islands or Asia.

Serum samples from 349 persons who had suspected dengue based on clinical presentation and onset of symptoms in 1997 and 1998 were submitted to CDC from 40 states and the District of Columbia. From these samples, 143 (38%) cases were laboratory diagnosed as dengue, 133 (93%) cases had IgM antibody in early convalescent samples or single high titers of IgG antibody in acute serum samples, and 10 (7%) cases had isolation of dengue virus. In three cases, positive by detection of anti-dengue IgM antibody, virus serotype was identified by polymerase chain reaction (PCR). Overall, DEN-4 was identified in five (39%) cases, DEN-2 in four (31%) cases, and DEN-1 and DEN-3 in two (15%) cases each. Dengue diagnosis was negative in 129 (37%) patients and indeterminate in 77 (22%) patients because convalescent samples for serologic testing were unavailable.

Of the 143 persons with laboratory-diagnosed dengue, sex was known for 130; 65 (50%) were males. Age was reported for 99 persons and ranged from age less than 1-70 years (median: 34 years). States reporting the highest number of cases were Florida (12) in 1997 and New York (22) in 1998. Travel histories within the 2 weeks before illness, available for 122 persons, indicated that infections probably were acquired in the Caribbean islands (61 cases), Asia (30), Central America (23),

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South America (four), Africa (three), and the Pacific islands (one). In 1998, 90 laboratory-diagnosed cases were reported, a 70% increase from the 53 cases reported in 1997. Among the 90 cases, 35 (39%) persons reported traveling to the Caribbean islands in 1998 compared with 14 (26%) in 1997.

Clinical information was available for 85 patients with laboratory-diagnosed dengue. Commonly reported symptoms were fever (94%), headache (69%), myalgia (53%), rash (53%), arthralgia (32%), retro-orbital pain (27%), nausea or vomiting (25%), chills (24%), diarrhea (19%), and petechiae or ecchymoses (15%). At least seven patients were hospitalized, and one patient died (diagnosed with DEN-2 by immunohistochemistry on autopsy tissue).

Reported by: State and territorial health departments. Infectious Disease Pathology Activity, Div of Viral and Rickettsial Diseases; Dengue Br, Div of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, CDC.

CDC Editorial Note: The principal vector of dengue is the mosquito Aedes aegypti, which has a wide distribution in most tropical and subtropical areas. In the United States, Aedes aegypti can be found during summer months in many states. Most U.S. residents with dengue become infected during travel to tropical areas, although autochthonous transmission of dengue was documented in Texas in 1999.2,3

The incubation period of dengue is 4-7 days (range: 3-14 days). Dengue virus infection can be asymptomatic or cause illnesses ranging from mild undifferentiated fever to severe disease, including hemorrhagic manifestations and shock.4 Dengue hemorrhagic fever (DHF) is characterized by fever, minor or major bleeding phenomena, thrombocytopenia (less than or equal to 100,000 platelets/mm3), and evidence of increased vascular permeability (eg, hemoconcentration [hematocrit increased by at least 20% from baseline], pleural or abdominal effusions, or hypoproteinemia).4 Dengue shock syndrome (DSS) is DHF with signs of circulatory failure, including narrow pulse pressure (less than or equal to 20 mm Hg), hypotension, or shock, and may result in death rates of approximately 10%.3

From 1993 through 1998, the number of imported laboratory-diagnosed U.S. cases increased, reflecting the impact of travel and the occurrence of epidemic activity, especially in the Caribbean and Central America. In 1998, laboratory-diagnosed cases of dengue were more than double the number reported in 1997. This pattern is consistent with the increased number of cases of dengue/DHF in the Americas for 1998 (741, 794) compared with 1997 (364, 945).8

The findings in this report are subject to at least two limitations. First, the number of dengue cases referred to CDC for diagnosis represents a minimum estimate of the actual number of U.S. travelers with dengue fever or its complication, DHF or DSS. Because dengue is not a nationally notifiable disease, diagnostic samples may not be sent for testing or may be sent to laboratories other than CDC; therefore, many imported cases may not be counted. For example, Florida implemented an active laboratory-based surveillance system from April 1, 1997, through March 31, 1998, which resulted in an increased detection of laboratory-positive cases from a previous 30-year annual mean of 1.4 cases to 18 cases during this period7; five of the 18 cases were reported from private clinical laboratories. Second, travel histories and clinical information were not available for all persons with dengue, and they may not be representative of all persons with imported dengue.

Persons traveling to areas where dengue is endemic should avoid exposure to mosquitoes by using repellents, wearing protective clothing, and remaining in well-screened or air-conditioned areas. No vaccine is available for preventing dengue infection. The Aedes aegypti mosquito is well adapted to urban environments and can be found in or near human dwellings, where the mosquito can be found in closets, bathrooms, behind curtains, and under beds. The species usually bites during the early morning and late afternoon, but may feed at any time during the day when indoors or during overcast periods.8

With an increase in traveling to and from endemic areas, more cases of imported dengue may be expected and health-care providers should consider dengue in the differential diagnosis of illness for all patients who have fever and a history of travel to tropical areas within 2 weeks before the onset of symptoms. Supportive measures should be given, and only acetaminophen is recommended for management of pain and fever. Acetylsalicylic acid (ie, aspirin) and other nonsteroidal anti-inflammatory agents are contraindicated because of their anticoagulant properties. Acute-phase and convalescent-phase serum samples should be obtained for viral isolation and diagnosis and sent for confirmation through state or territorial health departments to CDC’s Dengue Branch, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, CDC.

REFERENCES
1. CDC. Case definitions for infectious conditions under public health surveillance. MMWR 1997;46(no. RR-10):45-6.
Availability of Work-Related Lung Disease Surveillance Report, 1999

MMWR. 2000;49:235

CDC’s National Institute for Occupational Safety and Health (NIOSH) has released the Work-Related Lung Disease (WoRLD) Surveillance Report for 1999. This report is the fifth in a series of WoRLD reports presenting summary tables and figures concerning various occupationally relevant respiratory diseases, including pneumoconioses, occupational asthma, other airway diseases, and other respiratory conditions.

The WoRLD report presents national and state summary statistics such as counts, crude and age-adjusted mortality rates, and years of potential life lost to age 65 years and to life expectancy; U.S. maps showing the geographic distribution of mortality by state; and tables and figures summarizing selected occupational exposure data for asbestos, coal and coal mine dust, silica dust, cotton dust, and other substances. Proportionate mortality ratios by industry and occupation are based on the most recent decade of data from a subset of states for which usual industry and occupation have been coded for decedents. Also included are tables summarizing silicosis and asthma surveillance data collected by states funded by the Sentinel Event Notification Systems for Occupational Risks Program.

The 1999 WoRLD Surveillance Report is available from Surveillance Branch, Division of Respiratory Disease Studies, NIOSH, CDC, 1095 Willowdale Road, Morgantown, WV 26505-2888; fax (304) 285-6111; or e-mail WoRLD@cdc.gov.

REFERENCE

Satellite Broadcast on HIV Prevention

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“HIV Prevention With Incarcerated Persons,” a satellite broadcast, is scheduled for Thursday, April 27, 2000, at 1-3 PM eastern time. Co-sponsors are CDC and the Public Health Training Network. This forum will focus on activities and resources for human immunodeficiency virus (HIV) infection prevention within correctional facilities. Viewers will hear about CDC activities and programs throughout the country.

This broadcast is designed for organizations and persons involved in providing health care and HIV prevention for incarcerated persons and their partners. This audience includes administrators and other staff in correctional facilities, public health programs, community-based organizations, legislative staffs, and managed care. Speakers will discuss why incarceration is a critical opportunity for HIV prevention, benefits of HIV prevention for correctional programs and public health, specific programs in HIV prevention at correctional facilities, and resources and technical assistance for corrections and public health. Viewers can fax questions and comments before and during the satellite broadcast.

Additional information for organizations and potential viewers is available through the World-Wide Web site for this broadcast, http://www.cdcnpin.org/broadcast, and CDC’s Fax Information System, telephone (888) 232-3299 ([888] CDC-FAXX), by entering document number 130026 and a return fax number. Organizations setting up viewing sites can register online or by fax as early as possible so that potential viewers may access information about viewing locations when visiting the web site or calling the information line.

National Vaccine Program Office Workshop on Aluminum in Vaccines

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CDC’s National Vaccine Program Office will sponsor Workshop on Aluminum in Vaccines during May 11-12, 2000. The workshop will be held at the Caribe Hotel in San Juan, Puerto Rico, immediately following the Metal Ions in Biology and Medicine Conference. Discussion topics include vaccine adjuvants, aluminum salts in vaccines, the pharmacology and toxicology of aluminum, and macrophagic myofasciitis. Additional information is available on the World-Wide Web at http://www.cdc.gov/od/nvpo/calendar.htm, or telephone (404) 687-6672.