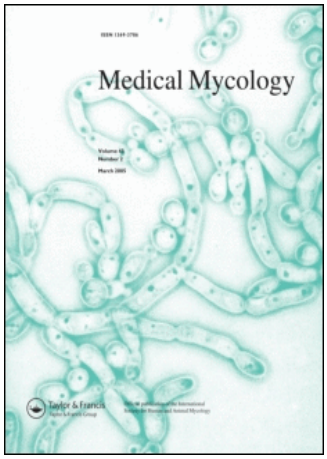

Medical Mycology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713694156

Histoplasmosis in Europe: Report on an epidemiological survey from the European Confederation of Medical Mycology Working Group

H. R. Ashbee [a]; E. G. V. Evans [b]; M. A. Viviani [c]; B. Dupont [d]; E. Chryssanthou [e]; I. Surmont [f]; A. Tomsikova [g]; P. Vachkov [h]; B. Ener [i]; J. Zala [j]; K. Tintelnot [k]; The ECMM Working Group On Histoplasmosis [k]

[a] Mycology Reference Centre, Department of Microbiology, Old Medical School, Leeds General Infirmary, Leeds, UK
[b] Formerly Welsh Mycology Reference Laboratory, Department of Medical Microbiology, University Hospital of Wales, Cardiff, UK
[c] Laboratorio di Micologia Medica, Dipartimento di Sanità Pubblica - Microbiologia - Virologia, Sezione di Sanità Pubblica, Università degli Studi di Milano, Italy
[d] Hopital Necker, Maladies infect. et tropicales, Paris, France
[e] Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden
[f] Heilig Hartziekenhuis, Roeselare, Belgium
[g] Institute of Microbiology, Plzen, Czech Republic
[h] Department of Infectious and Tropical Diseases, State University Hospital St Ivan Rieski, Sofia, Bulgaria
[i] Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Uludag, Gorukle, Bursa, Turkey
[j] Dept of Mycology, "Johan Bela" National Centre for Epidemiology, Budapest, Hungary
[k] Consultant Laboratory for Histoplasma capsulatum, Robert Koch-Institut, Berlin, Germany

First Published on: 18 September 2007
To cite this Article: Ashbee, H. R., Evans, E. G. V., Viviani, M. A., Dupont, B., Chryssanthou, E., Surmont, I., Tomsikova, A., Vachkov, P., Ener, B., Zala, J., Tintelnot, K. and Histoplasmosis, The ECMM Working Group On (2007) 'Histoplasmosis in Europe: Report on an epidemiological survey from the European Confederation of Medical Mycology Working Group', Medical Mycology, 46:1, 57 - 65
To link to this article: DOI: 10.1080/13693780701591481
URL: http://dx.doi.org/10.1080/13693780701591481

Medical Mycology February 2008, **46**, 57–65

informa
healthcare

Histoplasmosis in Europe: Report on an epidemiological survey from the European Confederation of Medical Mycology Working Group

H. R. ASHBEE*, E. G. V. EVANS†, M. A. VIVIANI‡, B. DUPONT§, E. CHRYSSANTHOU+, I. SURMONT¶, A. TOMSIKOVA Δ, P. VACHKOV□, B. ENER○, J. ZALA€, K. TINTELNOT◇ & THE ECMM WORKING GROUP ON HISTOPLASMOSIS

**Mycology Reference Centre, Department of Microbiology, Old Medical School, Leeds General Infirmary, Leeds, UK, †Formerly Welsh Mycology Reference Laboratory, Department of Medical Microbiology, University Hospital of Wales, Cardiff, UK, ‡Laboratorio di Micologia Medica, Dipartimento di Sanità Pubblica - Microbiologia - Virologia, Sezione di Sanità Pubblica, Università degli Studi di Milano, Italy, §Hopital Necker, Maladies infect. et tropicales, Paris, France, +Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden, ¶Heilig Hartziekenhuis, Roeselare, Belgium, ΔInstitute of Microbiology, Plzen, Czech Republic, □State University Hospital St Ivan Rieski, Department of Infectious and Tropical Diseases, Sofia, Bulgaria, ○Department of Microbiology and Infectious Diseases, Faculty of Medicine, University of Uludag, Gorukle, Bursa, Turkey, €Dept of Mycology, "Johan Bela" National Centre for Epidemiology, Budapest, Hungary, and ◇Robert Koch-Institut, Consultant Laboratory for Histoplasma capsulatum*, Berlin, Germany

The purpose of this survey was to systematically collect data on individuals with histoplasmosis in Europe over a 5-year period (from January 1995 to December 1999). This included information on where and how the infection was acquired, the patient's risk factors, the causative organism, how the infection was diagnosed and what therapy the patients received. Data were sent on a standardized survey form via a national convenor to the coordinator. During the survey, 118 cases were reported, with 62 patients having disseminated disease, 31 acute pulmonary infection, chronic pulmonary infection in 6 and localized disease in 2 patients. For 17 patients, the diagnosis of histoplasmosis was incidental, usually secondary to investigations for lung cancer. Most patients had travelled to known endemic areas, but 8 patients (from Italy, Germany and Turkey) indicated that they had not been outside their countries of origin and hence these cases appear to be autochthonous. Notable observations during the survey were the reactivation of the disease up to 50 years after the initial infection in some patients and transmission of the infection by a transplanted liver. Itraconazole was the most commonly used therapy in both pulmonary and disseminated disease. The observation of autochthonous cases of disease suggests that the endemic area of histoplasmosis is wider than classically reported and supports continued surveillance of the disease throughout Europe.

Keywords Histoplasmosis, diagnosis, epidemiology

Introduction

Histoplasmosis, caused by the thermally dimorphic fungus *Histoplasma capsulatum*, can affect both humans and animals. Histoplasmosis occurs in specific endemic areas, which are widespread and include North, Central and South America, Africa, India and Southeast Asia. Sporadic cases have also been reported

Received 27 March 2007; Accepted 24 July 2007
†Deceased
Correspondence: H. R. Ashbee, Mycology Reference Centre, Department of Microbiology, Old Medical School, Leeds General Infirmary, Leeds, LS1 3EX, UK. Tel: +44 (0)113 34928732. E-mail: h.r.ashbee@leeds.ac.uk

DOI: 10.1080/13693780701591481

in Europe. *H. capsulatum* occurs in the soil of endemic areas, especially those contaminated with bird and bat droppings [1]. Phylogenetic studies of *H. capsulatum* have identified at least eight clades, which correspond to different geographic regions [2]. The African clade includes those isolates previously classed as *H. capsulatum* var. *duboisii* as well as those classed as *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *farciminosum*.

Over 95% of healthy people who are exposed to a low inoculum of *H. capsulatum* conidia will remain asymptomatic [3]. Those immunocompetent patients that do develop symptoms, most commonly present with acute pulmonary histoplasmosis, a 'flu-like' illness. Exposure to a high level of *H. capsulatum* conidia in healthy people will cause symptomatic disease in 50–100% of them [3]. Patients who have pre-existing lung damage may develop chronic pulmonary histoplasmosis. This form is difficult to distinguish from tuberculosis and presents with recurrent pulmonary symptoms, progressive fibrosis and cavitation. Disseminated histoplasmosis usually occurs at the extremes of age or in patients who have cell-mediated immune deficiencies, including AIDS, lymphoma or patients who are receiving immunosuppressive therapy [4]. Reactivation of disease many years after primary infection may occur in patients who become immunosuppressed or even in apparently normal hosts, due to the intracellular survival of *H. capsulatum* in the reticuloendothelial system. Antifungal therapy is mandatory for disseminated disease, followed by lifelong maintenance therapy in patients with cellular immunodeficiency. However, discontinuation of maintenance therapy in patients with AIDS responding to antiretrovirals is under discussion [5].

Most reported cases of histoplasmosis in Europe are in immigrants or people returning from highly endemic areas [6]. However, there have been reports of cases in patients who have not travelled outside their country of origin, namely patients from the UK and Italy [7,8]. Prior to the present survey, there have been 8 cases of histoplasmosis in Italians that are believed to be autochthonous.

In March 1997, the European Confederation of Medical Mycology convened a working group to study the epidemiology of histoplasmosis in Europe. The aims of the survey were to obtain an overview of the incidence of the disease in Europe, to define where and how the infection was acquired, to determine whether other autochthonous cases had occurred within Europe, the groups at risk, the causative organism, methods by which the infection was diagnosed and what therapy patients received.

Patients and methods

All countries in Europe who are affiliated to the European Confederation of Medical Mycology (ECMM) were invited to participate and those who appointed a national convenor are listed in Table 1. Specific guidelines on how to collect these data in each country were not provided. A standardized survey form was designed to record data on the risk factors, travel history, signs and symptoms, method of diagnosis and therapy for each subject and was published in the ECMM Newsletter in 1997.

The presence of risk factors to be noted included HIV infection, corticosteroid therapy, malignancy, transplantation, travel to known endemic areas and exposure to possible reservoirs of *H. capsulatum.* The clinical presentation of the infection, the findings on imaging and the diagnostic methodology (including the use of histology, culture and serology) that resulted in a diagnosis of suspected histoplasmosis were requested. Since DNA detection from clinical samples had not yet been established as a routine method, molecular methods were not included in the questionnaire. Finally, information on the therapy that the individual received was also requested. The survey form did not collect information about disease outcome.

Cases were reported to the convenor in each country who eliminated identifiers, assigning a country code and a code number for each patient prior to forwarding the data to the European convenor.

The survey was carried out over a 5-year period, with information collected retrospectively from January

Table 1 Cases of histoplasmosis in contributing countries occurring during the retrospective (Jan 95–Dec 97) and prospective (Jan 98–Dec 99) phases of the survey.

	Retrospective	Prospective	Total
Germany	23	23	46
Italy	14	8	22
United Kingdom	10	9	19
France	8	2	10
Belgium	1	5	6
Sweden	5	1	6
Switzerland	0	4	4
Austria	1	1	2
Bulgaria	2	0	2
Turkey	1	0	1
Total	65	53	118

Reports from Czech Republic and Hungary were possible cases and had to be excluded. Countries that appointed a national convenor but either had no cases of histoplasmosis or did not submit any data are Denmark, Greece, Israel, The Netherlands, Poland, Portugal, Russia and Spain.

1995 to December 1997 and prospectively from January 1998 to December 1999.

The following definitions were used to categorize individuals with histoplasmosis:

- Proven – *H. capsulatum* was cultured from or identified in tissue from any site; if isolated from sputum or bronchoalveolar lavage (BAL), patients also had clinical symptoms indicative of pulmonary histoplasmosis. Microscopically detected organisms compatible with *H. capsulatum* in BAL or sputum without culture were not accepted as proven, due to a possible confusion with small celled yeasts such as *Candida glabrata*.
- Probable – the individual had a travel history to a known endemic area, the presence of positive serological tests and imaging of the lung revealed lesions consistent with histoplasmosis.
- Possible – the individual had a travel history to a known endemic area and either positive serological tests or imaging of the lung revealed lesions consistent with histoplasmosis.

The following definitions were also used with regard to disease presentation:

- Acute pulmonary – patients presenting with an acute primary infection after recent exposure to *H. capsulatum* risk factors.
- Chronic pulmonary – patients who had suffered from the disease for more than 6 months and were still symptomatic.
- Pulmonary (incidental finding) – patients in whom the finding of pulmonary histoplasmosis was incidental after investigations for other diseases, e.g. lung cancer.
- Disseminated – systemic disease occurring at multiple sites.
- Localized – patients who only had localized lesions secondary to trauma without indication of primary pulmonary disease.

Results

Over the 5-year period 128 cases of histoplasmosis were reported from 12 countries (Table 1). Another 8 countries that had appointed a national convenor, either had no cases of histoplasmosis during the study period or did not return survey forms. Only 118 of the 128 cases met the criteria for proven (92 patients) or probable (26 patients) histoplasmosis to be included in this investigation. The majority of cases occurred in males (75%), with half of the individuals in the age range 21–40 years (Fig. 1). Sixty-two of 118 patients (53%) had disseminated disease, i.e. acute pulmonary infection occurred in 31 (26%), chronic pulmonary in 6 (5%) and localized disease in two patients. For 17 patients the finding that they had histoplasmosis was incidental and occurred after investigations usually for suspected lung cancer. The travel history or country of origin of individuals included West Africa ($n=15$), Central Africa ($n=8$), Southern Africa ($n=4$), Eastern Africa ($n=2$), "Africa" ($n=3$), North America ($n=5$), Central America ($n=27$), South America ($n=31$), India, Pakistan and Myanmar ($n=6$), China ($n=1$), South East Asia ($n=2$) and for 2 patients travel was to "endemic areas". For the five individuals whose travel history was either not known or not specified, there is

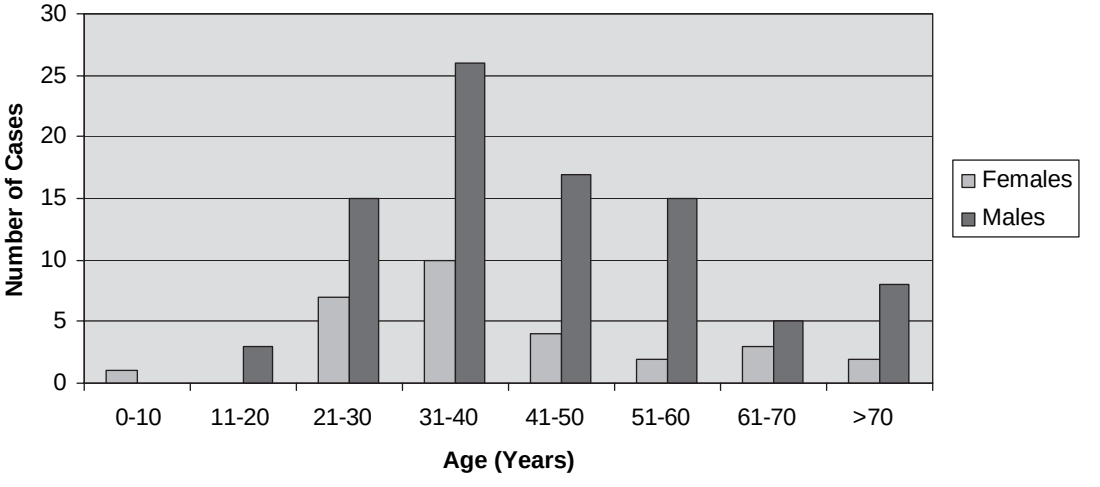

Fig. 1 Age and sex of patients with histoplasmosis.

the possibility that they have travelled to endemic areas. However, eight patients had no history of travel outside their country of origin. These individuals were natives of Italy ($n=5$), Germany ($n=1$), Turkey ($n=1$) and France ($n=1$).

The risk factors for histoplasmosis were varied (Table 2). Most individuals had travelled to endemic areas, and whilst there they were exposed to bats and/or had visited caves.

The period between travel to endemic areas and the start of clinical symptoms varied considerably. For 26 individuals (22%), symptoms developed within 2 months of travel and these were considered primary infections. In 36 others (31%), symptoms occurred within 2 months to 5 years of travel. For another 29 patients (25%), symptoms did not occur for at least 5 years after travel and in 27 (including those without history of travel; 23%) the latency period was unknown. For 43% of patients with pulmonary infections, symptoms began within 2 months of travel, and a further 35% of these individuals developed symptoms within 2 months to 5 years. In most of these patients, this represents the acute pulmonary form of infection. However, 41% of those with disseminated disease represented reactivation of histoplasmosis more than 5 years after travel to endemic areas.

HIV-infection was the most important underlying disease ($n=43$) and 42 of the HIV positive patients had disseminated disease. For those where the CD4 count was known ($n=38$), 36 had a CD4 count $<150\ mm^{-3}$. Other underlying diseases or predisposing factors in disseminated disease included chronic obstructive pulmonary disease (COPD; $n=2$), leukaemia ($n=1$), liver transplantation ($n=1$) and SLE ($n=1$).

Two patients who had localized disease due to the apparent direct inoculation of *H. capsulatum* secondary to trauma had no associated evidence of systemic disease. In one of these, the patient (a native of Italy) had no history of travel and hence it appears to be an autochthonous case. The second patient was a 29-year-old male from Togo in Africa, who had no underlying disease but a localized infection of the skin at his left shoulder with osteitis. Antibody detection was negative but a large-celled histoplasmosis (previous *H. capsulatum* var. *duboisii*) was identified histologically.

Table 2 Risk factors for histoplasmosis to which patients were exposed.

Risk factor (s)	No. of patients
Travel or residence in known endemic area of whom	106
HIV infection	45
Exposure to birds, bats, caves	26
Corticosteroid therapy	7
Malignancy	2
Recipient of an infected liver	1
Unknown risk factors	
Data not reported	1
Travel history unknown	4
No known risk factors	7

The signs and symptoms obviously differed between individuals with pulmonary histoplasmosis and disseminated histoplasmosis. Most common was fever (50% and 52%) in both groups, followed by cough (44%) in individuals with pulmonary disease and weight loss (24%) and skin lesions (23%) in patients with disseminated histoplasmosis. However, most patients had multiple symptoms.

The methods by which the diagnosis of histoplasmosis was made varied considerably among the participating countries (data not shown), as well as with patients with pulmonary and disseminated disease. In many instances more than one method was used to establish the diagnosis (Table 3). Serological testing included antibody detection by immunodiffusion, complement fixation tests, western blotting and/or antigen testing (one case only) and was carried out in all but two of the countries that contributed cases. Antibody detection contributed to the diagnosis in 27 of the 38 patients with pulmonary disease in whom it was carried out and in 17 of the 27 individuals tested with disseminated disease. Culture and histology were commonly used to diagnose disseminated disease, with positive results found in 71% and 68% of patients, respectively. In 20 of 62 individuals with disseminated disease, the diagnosis was established by culture alone, in 18 others by histology alone and in 24 patients by both culture and histology. The sites from which samples were obtained that subsequently proved positive by culture and histology for patients with disseminated disease are shown in Table 4.

In contrast, culture and histology were positive in patients with pulmonary disease in 16 and 41% of cases, respectively. In 7 of the cases, the diagnosis was established by culture alone, in 21 by histology alone and by both for 2 patients.

Itraconazole was the most commonly used antifungal being employed in the treatment of 19 patients with pulmonary infections and 43 patients with disseminated disease. However, amphotericin B was also commonly used in disseminated disease ($n=33$; 53%). Many patients received several different antifungals sequentially, depending on disease control and patient tolerance of the drug. Three patients with disseminated disease received no therapy, either because the correct

Table 3 Positive diagnostic tests (as a percentage of those patients tested) that contributed to a diagnosis of histoplasmosis[1].

Method	Acute pulmonary ($n=31$)	Chronic pulmonary ($n=6$)	Pulmonary (incidental finding, $n=17$)	Disseminated ($n=62$)
Histology	6 (100%)	2 (100%)	15 (100%)	42[2] (100%)
Culture	5 (31%)	4 (80%)	0 (0/1)	44 (83%)
Antigen	–	–	–	1 (50%)
Antibodies (any method)	24 (89%)	1 (50%)	5 (50%)	17 (28%)
Antibody				
ID	19 (76%)	1 (100%)	1 (15%)	14 (37%)
CFT	9 (90%)	1 (100%)	1 (100%)	8 (47%)
WB	9 (90%)	0 (0/1)	5 (83%)	4 (67%)
Skin test	0	1 (100%)	1 (100%)	–
Imaging	31 (100%)	6 (100%)	15 (100%)	29 (91%)

ID, Immunodiffusion; CFT, Complement fixation test; WB, Western blot.
[1]Patients may have been diagnosed by more than one method.
[2]Infection due to *H. capsulatum* var *duboisii* diagnosed in 3 patients.

diagnosis was made too late and they died before therapy could be instituted, or because the disease was misdiagnosed.

Discussion

This survey aimed to collect and evaluate as many cases as possible of histoplasmosis that occurred in Europe over a 5-year period. However, it should be noted that the results of the survey may be affected by the fact that histoplasmosis is rarely taken into consideration as part of the differential diagnosis in Europe, most infections are self-limiting in immunocompetent hosts and collection and reporting of data depend on the interest of clinicians and microbiologists.

Table 4 Sites in patients with disseminated histoplasmosis ($n=62$) from which culture and/or histology were positive (for some patients culture and/or histology was positive at more than one site).

Site	No. positive for culture	No. positive for histology[1]
Blood	18	1
Skin	8	13
Lymph nodes	9	6
Oral lesions	5	6
Bone marrow	8	3
Gastrointestinal	1	6
Lungs	2	5
BAL/Sputum	5	1
Liver	–	5[2]
Adrenal glands	1	5
Bone or joint	2	2
Pus or abscess	2	3
Urine	2	–
Oesophagus	1	–
Spleen	–	3[2]
CSF	1	–
Ascites	1	–

[1]One patient also had positive histology at 'disseminated sites'.
[2]All specimens studied post mortem.

In addition to the 118 cases reported here, it is known that others occurred during the survey period but the authors did not submit their data to the ECMM working group [9]. The results presented here do not allow an accurate assessment of the incidence of histoplasmosis in Europe during the survey period but rather reflect the patients' travel habits and ease of access to diagnostic facilities, as well as the index of suspicion for histoplasmosis in the countries that were involved in the survey. The relatively high number of case reports from Germany might be due to a request to over 500 German pathologists to participate in this survey, some of whom sent several reports of incidental finding in lung residues of histoplasmosis.

Several findings seen in this study are already known from epidemiological studies of histoplasmosis in endemic areas [1]. The majority of the cases occurred in males [1], and this was true for both the pulmonary and disseminated disease. However, this difference is thought to be the result of differential exposure, rather than an innate difference in susceptibility between the sexes. Additionally, the proportion of male patients with disseminated histoplasmosis is due to the high percentage of HIV in these individuals. Similar results were recently reported in reviews on histoplasmosis and cryptococcosis in AIDS patient in Europe [10,11]. The high number of patients between the ages of 21 and 40 (almost half of the cases in our survey) is comparable with previously reported peaks of acute histoplasmosis in individuals aged 15–34 [12]. These cases may be due to the patients' participation in outdoor activities through which they were at greater risk of exposure to the fungus. However, a noticeable feature of several patients reported in this survey was that they developed

disseminated histoplasmosis as they grew older. This may be as a result of their general failing health and/or diminished immune surveillance. Since most of these elderly patients did not live in endemic areas, they had not developed immunity to the disease. Consequently, the occurrence of histoplasmosis in these patients was probably the result of reactivation of their initial primary infection. Recently, fungal infections have been noted as becoming an increasing problem in older patients [13].

Most risk factors to which patients had been exposed were those known to predispose to histoplasmosis. All but 8 of the patients studied had travelled to or lived in known endemic areas, most frequently in Africa and South America. Visiting caves in endemic areas is an emerging risk factor for exposure to *H. capsulatum*, especially if carried out without masks. Many of the patients who presented with acute pulmonary disease were cavers who had explored bat infested caves in Cuba [14] or Costa Rica. For 2 patients with disseminated disease, 4 with pulmonary histoplasmosis and 1 with localized disease there was no history of travel to endemic areas nor was any other predisposing factors identified. Since these patients originated from Italy, Germany and Turkey, they seem to have acquired their disease in countries not generally thought to be endemic for histoplasmosis. Another possible, but unlikely explanation is that these patients were exposed to fomites contaminated with the conidia of *H. capsulatum* from which they contracted the disease. There have been several reports from Italy, mainly from Lombardia and Emilia Romagna, of autochthonous histoplasmosis [15–19] and *H. capsulatum* has been recovered from soil [20] and dogs [21] in Italy. A single histologically proven case of histoplasmosis from a Turkish patient has previously been described [22] and *H. capsulatum* has been isolated from the environment in Turkey [23]. Although autochthonous cases of histoplasmosis have not previously been seen in Germany, fungi highly likely to be *H. capsulatum* have been detected in histological samples from badgers [24], suggesting that there might be an environmental reservoir of the fungus. Nevertheless it cannot be excluded that the patient had travelled to Italy. It has been the experience of several authors that patients may deny travel outside their home country when initially interviewed. However, subsequently questioning of these same individuals will find that they had travelled, often years previously. Thus, obtaining a lifelong history from patients is critical.

Obviously, the period of latency between travel to endemic area and development of signs and symptoms of histoplasmosis was different for those patients with pulmonary disease as compared with those with extra pulmonary dissemination. Interestingly, several of the cases of disseminated disease reported from the UK occurred in elderly men who had served in World War II in India and Myanmar (previously Burma). These individuals had been residents of the UK after the war, indicating a latency period in excess of 50 years. Long latency periods have been reported by other groups, e.g. a latency period of 10 years was described in an immunocompetent patient who had previously been resident in Africa [25]. Histoplasmosis occurs in many parts of India [26] and Bangladesh and has been reported in individuals from Myanmar [27]. Since *Histoplasma* has been isolated from the soil of West Bengal [28], India and perhaps other adjacent countries, should be regarded as endemic areas.

Although one French patient was notable in having no travel to endemic areas he developed disseminated histoplasmosis after he had received a liver transplant from a donor who had previously resided in an endemic area and probably acquired the disease from the transplanted organ. This has been reported previously with patients contracting the disease from transplanted kidneys [29–32] and liver [33].

Signs and symptoms of disease were quite variable, with 9 patients with pulmonary disease being asymptomatic. For asymptomatic individuals, the diagnosis was often made accidentally as a result of screening for cancer by chest X-rays. Similar findings have also been noted in patients with cryptococcomas detected on chest X-ray.

H. capsulatum var. *duboisii* was reported as the infectious agent in 5 patients with skin, bone or oral lesions, all of whom had either travelled to or were natives of Africa or the Middle East. As previously discussed, a recent analysis of sequence variations of 137 *Histoplasma* isolates from different geographical areas revealed *H. capsulatum* was composed of multiple clades and concluded that the assignment of three varieties of *H. capsulatum* (including *H. capsulatum*. var. *farciminosum* in horses and *H.capsulatum* var *duboisii*) was not phylogenetically relevant [2]. Currently, the only correlate for the identification of *H. capsulatum* var *duboisii* seems to be the histologic detection of large *H. capsulatum* cells, as reported in five of the patients in this survey. *H. capsulatum* var *capsulatum* was found in this survey to be the etiologic agent in 27 of 32 patients who originated from Africa. In conclusion, this analysis suggests that African patients cannot be assumed per se to be infected with *H. capsulatum* var. *duboisii* and should especially not be described as having 'African histoplasmosis'.

Ocular histoplasmosis was never noted, even in patients with disseminated disease. Dissemination of *H. capsulatum* to the eye is rare and the diagnosis of 'presumed ocular histoplasmosis' is unlikely to be related to infection with this organism [34,35].

Although serologic studies were helpful, imaging was the most common diagnostic method used in the pulmonary form of the disease. Since the appearance of histoplasmosis on chest X-ray is not always characteristic of the disease, diagnosis requires other forms of evidence. The formation of histoplasmomas, in particular those not yet calcified and in the lower lobes of the lungs, may prompt investigations for lung carcinomas, especially in older patients who were not aware of a previous episode of histoplasmosis. This was the case in several patients in this study who underwent surgery for presumed carcinoma of the lung, only to be diagnosed with histoplasmosis on histological grounds. In such individuals, obtaining a travel history and performing serological investigations for histoplasmosis may prevent unnecessary surgery and provide a diagnosis. Various serological tests are routinely used for diagnosis of histoplasmosis, including immunodiffusion and complement fixation. Western blot and antigen detection are not commercially available in many European countries and those methods that were available differed among the participating countries. For example, Western blot was commonly used due to its increased sensitivity compared to the immunodiffusion in the Consultant Laboratory for *H. capsulatum* in Germany [36,37], but was not employed in other countries. Detection of antibodies against *H. capsulatum* contributed to the diagnosis in more patients with pulmonary disease than those with disseminated infections. This may be a reflection of the immunological compromise condition of many patients who had disseminated disease in whom antibody production was probably limited. In the latter patients, culture and histological diagnosis was more helpful, correlating with the results from previous studies in which cultures were positive in 50–85% of patients with disseminated disease [38]. Cultures were most commonly positive from blood in patients with disseminated disease and so it would appear that blood may be an effective means of diagnosing disseminated disease. Unfortunately no questions relative to the specific blood culture systems which contributed to the positive detection of the fungus were included in our survey form. However, the isolator blood culture system has been shown to be more reliable to detect *Histoplasma* than BACTEC bottles [39]. Obviously in immunocompetent patients who develop acute pulmonary disease it is often not possible to culture the organism and other methods of diagnosis must be employed. The skin test, which has been developed for epidemiological studies, was also a good indicator for the diagnosis of *H. capsulatum* infection in patients from outside of endemic areas [9,40,41]. Unfortunately, this test is no longer commercially available.

While the therapy which patients received varied in Europe, itraconazole was the most widely used drug for both pulmonary and disseminated disease. However, the current IDSA guidelines recommend the use of amphotericin B as first line therapy for severe disseminated disease. Itraconazole is suitable for less severe disseminated disease and mild – moderate pulmonary disease [42].

One noticeable finding during the collection of the data was the ease with which it could be obtained varied from country to country. In some countries, it was difficult for the convenor to obtain information about cases because the necessary networks and health surveillance facilities were not in place. This obviously limits the accuracy of the data from these countries and consequently, this survey may not accurately reflect the incidence of histoplasmosis in Europe. As the majority of infections with *H. capsulatum* in immunocompetent people are usually clinically asymptomatic, we can speculate that thousands of Europeans are infected by *H. capsulatum* every year by travelling to endemic areas outside of Europe. The occurrence of several autochtonous infections, especially in Southern Europe and European countries with badgers, suggests that continuing the documentation of further case reports of histoplasmosis in Europe is worthwhile.

In conclusion, clinicians as well as pathologists in Europe should be aware of histoplasmosis, especially in immunocompromised patients, organ transplant recipients and in AIDS patients from outside Europe [10] who are not receiving antiretrovirals. Reactivation of disease decades after the primary infection, as well as histoplasmosis acquired due to organ transplantation are striking findings of this survey. Diagnosing an infection as being due to *H. capsulatum*, e.g. by detection of specific antibodies and documentation of the results for the patient, even in cases of mild, self-limited pulmonary histoplasmosis, might be beneficial, especially if the person becomes immunocompromised later in their life. This may provide subsequent physicians with sufficient information to be able to diagnosis reactivation of the disease. The widespread use of sensitive diagnostic methods, including Western blot for antibody detection in areas not endemic for *H. capsulatum*, or molecular methods, will improve our ability to diagnose this disease rapidly and reliably and hence improve patient outcome. The creation of a

European reference centre able to perform antibody, antigen and PCR diagnosis of this disease would be a possible solution to the variation in methodology and difficulty of diagnosing the disease in individual European countries.

Acknowledgements

The ECMM Working Group consists of the following members:
Austria: S. Knapp, E. Presterl, B. Willinger (Wien)
Belgium: C. Trolin, D. Dechamps (Brussels), S. Weegemans (Antwerp), M. Haerens (Kortrijk), R. Ryckaert (Sint Niklaas), G. Claeys (Gent)
France: P. Vilde, F. Botterel (Paris)
Germany: H. Knechten (Aachen); W. Heise, M. Hussels, H. Lode, Marini-Sarianidis, N. Schönfeld, Stolzes (Berlin); A. Sählbrandt, C. Woll (Bottrop); B. Baumgarten (Erlangen); H. Schöfer (Frankfurt); R. Heine (Halle); U. Degen, I. Sobottka, H. Sudeck, A. Wywiol (Hamburg); A. Mosthaf (Karlsruhe); P. Harten (Kiel); P. Nenoff, S. Schubert (Leipzig); F. Petry, Schneider (Mainz); T. Grünewald (Minden); A. Morresi-Hauf, S. v. Pusch, J. Sklarek, O. Weeg (München); F. Strahlendorf-Elsner (Neumünster); K. Erkens (Rostock); G. Schulz (Sommerfeld); K. Fleischer, H. Klinker, M. Weig (Würzburg)
Italy: C. Farina (Bergamo); A.Chiodera (Brescia); E.Faggi (Firenze); S. Antinori, P. L. Oreste, R. Pometta, G. Vago, M. G. Viganò (Milano) ; F. Rivasi (Modena); G. Morace, V. Vullo (Roma); L. Laurini (Siena); P. G. Scotton (Treviso)
Sweden: P. Runnow (Huddinge), P. Forsberg (Vaxjo), B. Petrini (Stockholm), C. Holman
Switzerland: A. C. Guex (Basel); G. Schär (Zürich)
United Kingdom: B. O'Connell (Cambridge), R. Lewis (Glasgow), N. Fernando (Welwyn Garden City), K. McLaren (Edinburgh), J. Graham (Newcastle), C. Theodore (Croydon), S. Chapman (Isle of Wight), A. Pillai (Birmingham), W. Shattles (Crawley), N. Beeching (Liverpool), R. Hay (Belfast), P. McWhinney (Bradford), S. Green (Sheffield), N. Shetty, C. Taylor, I. Cropley, S. Lucas, R. Holliman, S. Eykyn, K. Knox (London)

The authors would like to thank Prof Mary Mathews for advice on histoplasmosis in India.

References

1 Cano MVC, Hajjeh RA. The epidemiology of histoplasmosis: a review. *Sem Resp Inf* 2001; **16**: 109–118.
2 Kasuga T, White TJ, Koenig G, *et al*. Phylogeography of the fungal pathogen *Histoplasma capsulatum*. *Mol Ecol* 2003; **12**: 3383–3401.
3 Goldman M, Johnson PC, Sarosi GA. Fungal pneumonias. The endemic mycoses. *Clin Chest Med* 1999; **20**: 507–519.
4 Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev* 2007; **20**: 115–132.
5 Goldman M, Zackin R, Fichtenbaum CJ, *et al*. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Inf Dis* 2004; **38**: 1485–1489.
6 Manfredi R, Mazzoni A, Nanetti A, *et al*. *Histoplasmosis capsulati* and *duboisii* in Europe: the impact of the HIV pandemic, travel and immigration. *Eur J Epidemiol* 1994; **10**: 675–681.
7 Symmers WC. Histoplasmosis contracted in Britain. *Br Med J* 1956; 786–790.
8 Viviani MA, Vago G, Farina C, *et al*. ECMM Survey of Histoplasmosis in Europe. Report from Italy. *Rev Iberoamer Micol* 2000; **17**: S143.
9 Gascon J, Torres JM, Luburich P, *et al*. Imported histoplasmosis in Spain. *J Travel Med* 2000; **7**: 89–91.
10 Antinori S, Magni C, Nebuloni M, *et al*. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. *Medicine* (Baltimore) 2006; **85**: 22–36.
11 Viviani MA, Cogliati M, Esposto MC, *et al*. Molecular analysis of 311 *Cryptococcus neoformans* isolates from a 30-month ECMM survey of cryptococcosis in Europe. *FEMS Yeast Res* 2006; **6**: 614–619.
12 Wheat LJ, Slama TG, Eitzen HE, *et al*. A large urban outbreak of histoplasmosis: clinical features. *Ann Intern Med* 1981; **94**: 331–337.
13 Kauffman CA. Fungal infections in older adults. *Clin Infect Dis* 2001; **33**: 550–555.
14 Erkens K, Lademann M, Tintelnot K, *et al*. [Histoplasmosis group disease in bat researchers returning from Cuba]. *Dtsch Med Wochenschr* 2002; **127**: 21–25.
15 Antinori S, Galimberti L, Bonaccorso C, *et al*. A case of fatal disseminated histoplasmosis of autochthonous origin in an Italian AIDS patient. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 545–546.
16 Romano C, Castelli A, Laurini L, *et al*. Case report. Primary cutaneous histoplasmosis in an immunosuppressed patient. *Mycoses* 2000; **43**: 151–154.
17 Sotgiu G, Mantovani A, Mazzoni A. Histoplasmosis in Europe. *Mycopathol Mycol Appl* 1970; **41**: 53–74.
18 Farina C, Gnecchi F, Michetti G, *et al*. Imported and autochthonous histoplasmosis in Bergamo province, Northern Italy. *Scand J Infect Dis* 2000; **32**: 271–274.
19 Calza L, Manfredi R, Donzelli C, *et al*. Disseminated histoplasmosis with atypical cutaneous lesions in an Italian HIV-infected patient: another autochtonous case. *HIV Med* 2003; **4**: 145–148.
20 Sotgiu G, Mazzoni A, Mantovani A, *et al*. Survey of soils for human pathogenic fungi from the Emilia-Romagna region of Italy. *Am J Epidemiol* 1966; **83**: 329–337.
21 Mantovani A, Mazzoni A, Ajello L. Histoplasmosis in Italy. I. Isolation of *Histoplasma capsulatum* from dogs in the provence of Bologna. *Sabourdia* 1968; **6**: 163–164.
22 Saglam T. Histoplasmosis. *Schweiz Med Wschr* 1946; **76**: 1153–1156.
23 Yucel A, Kantarcioglu AS. A detailed study on a *Histoplasma capsulatum* strain isolated in Turkey. *Turkiye Parazitoloji Dergisi* 1999; **23**: 62–71.
24 Grosse G, Staib F, Rapp J, *et al*. Pathological and epidemiological aspects of skin lesions in histoplasmosis. *Zentral Bakteriol* 1997; **285**: 531–539.

25 Desmet P, Vogelaers D, Afschrift M. Progressive disseminated histoplasmosis 10 years after return out of Africa in an immunocompetent host. *Acta Clin Belg* 2004; **59**: 274–278.
26 Subramanian S, Abraham OC, Rupali P, *et al*. Disseminated histoplasmosis. *J Assoc Physicians India* 2005; **53**: 185–189.
27 Hung MN, Sun HY, Hsueh PR, *et al*. Meningitis due to *Histoplasma capsulatum* and *Mycobacterium tuberculosis* in a returned traveler with acquired immunodeficiency syndrome. *J Formosa Med Assoc* 2005; **104**: 860–863.
28 Sanyal M, Thammayya A. *Histoplasma capsulatum* in the soil of Gangetic Plain in India. *Indian J Med Res* 1975; **63**: 1020–1028.
29 Limaye AP, Connolly PA, Sagar M, *et al*. Transmission of *Histoplasma capsulatum* by organ transplantation. *New Engl J Med* 2000; **343**: 1163–1166.
30 Watanabe M, Hotchi M, Nagasaki M. An autopsy case of disseminated histoplasmosis probably due to infection from a renal allograft. *Acta Pathol Jpn* 1988; **38**: 769–780.
31 Wong SY, Allen DM. Transmission of disseminated histoplasmosis via cadaveric renal transplantation: case report. *Clin Infect Dis* 1992; **14**: 232–234.
32 Hood AB, Inglis FG, Lowenstein L, *et al*. Histoplasmosis and thrombocytopenic purpura: transmission by renal homotransplantation. *Can Med Assoc J* 1965; **93**: 587–592.
33 Botterel F, Romand S, Saliba F, *et al*. A case of disseminated histoplasmosis likely due to infection from a liver allograft. *Eur J Clin Microbiol Inf Dis* 1999; **18**: 662–664.
34 Braunstein RA, Rosen DA, Bird AC. Ocular histoplasmosis syndrome in the United Kingdom. *Br J Ophthalmol* 1974; **58**: 893–898.
35 Suttorp-Schulten MS. The etiology of the presumed ocular histoplasmosis syndrome. *Ocul Immunol Inflamm* 1997; **5**: 71–72.
36 Pizzini CV, Zancope-Oliveira RM, Reiss E, *et al*. Evaluation of a western blot test in an outbreak of acute pulmonary histoplasmosis. *Clin Diagn Lab Immunol* 1999; **6**: 20–23.
37 Leimann BC, Pizzini CV, Muniz MM, *et al*. Histoplasmosis in a Brazilian center: clinical forms and laboratory tests. *Rev Iberoam Micol* 2005; **22**: 141–146.
38 Tewari R, Wheat LJ, Ajello L. Agents of histoplasmosis. In: Topley WWC, Wilson GS, Ajello L, Hay RJ (eds). *Topley and Wilson's Microbiology and Microbial Infections,* 9th edn. *Medical Mycology v. 4*. London: Hodder and Stoughton. 1998: 373–393.
39 Vetter E, Torgerson C, Feuker A, *et al*. Comparison of the BACTEC MYCO/F Lytic bottle to the isolator tube, BACTEC Plus Aerobic F/bottle, and BACTEC Anaerobic Lytic/10 bottle and comparison of the BACTEC Plus Aerobic F/bottle to the Isolator tube for recovery of bacteria, mycobacteria, and fungi from blood. *J Clin Microbiol* 2001; **39**: 4380–4386.
40 Confalonieri M, Gandola L, Aiolfi S, *et al*. Histoplasmin sensitivity among a student population in Crema, Po Valley, Italy. *New Microbiol* 1994; **17**: 151–153.
41 Wen FQ, Sun YD, Watanabe K, *et al*. Prevalence of histoplasmin sensitivity in healthy adults and tuberculosis patients in southwest China. *J Med Vet Mycol* 1996; **34**: 171–174.
42 Wheat J, Sarosi G, McKinsey D, *et al*. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. *Clin Infect Dis* 2000; **30**: 688–695.