



Original Article

Epidemiological Characterization of Imported Systemic Mycoses Occurred in Korea

Seung-Hak Cho ^{a,†}, Young-Bin Yu ^{b,‡}, Je-Seop Park ^c, Keun-Dol Yook ^{d,‡}, Young-Kwon Kim ^{b,‡,*}

^a Division of Bacterial Disease Research, Center for Infectious Disease Research, Korea National Institute of Health, Cheongju, Korea

^b Department of Biomedical Laboratory Science, College of Medical Sciences, Konyang University, Daejeon, Korea

^c Fire Science Laboratory, National Fire Service Academy, Asan, Korea

^d Department of Clinical Laboratory Science, Daejeon Health College, Daejeon, Korea

ABSTRACT

Article history:

Received: August 18, 2018

Revised: September 8, 2018

Accepted: September 13, 2018

Keywords:

blastomycosis,
coccidioidomycosis,
epidemiology,
histoplasmosis, mycoses

Objectives: Imported systemic mycoses is a severe fungal infection that can cause diseases in healthy people. However, there is a serious lack of epidemiological data about imported systemic mycoses. Therefore, an epidemiological characterization of imported systemic mycoses in Korea was performed.

Methods: We collected health insurance data between 2008 and 2012 from the Health Insurance Corporation and analyzed the data to determine the prevalence and treatment management of imported systemic mycoses.

Results: The prevalence of imported systemic mycoses between 2008 and 2012 increased slowly by 0.49/100,000 to 0.53/100,000 persons. The prevalence of coccidioidomycosis increased from 0.28/100,000 in 2008 to 0.36/100,000 persons in 2012. A mean of 229.6 cases occurred each year. Children and the elderly showed higher prevalence than adults in the 20- to 59-year-old age group. The rate of infection according to region ranged from 0.18/100,000 persons in Ulsan, to 0.59/100,000 persons in Gyeonggi. The prevalence in females was higher than that in males. Inpatient treatment was 3.3% (38 cases), with 96.7% treated as outpatients. Hospitalizations cost 272.7 million won and outpatient treatments cost 111.7 million won. The treatment cost for coccidioidomycosis from 2008 to 2012 was 330.9 million won, with personal charges of 79.2 million won and insurance charges of 251.7 million won. Most of the expenses for the coccidioidomycosis treatment were for inpatient treatment.

Conclusion: The results in this study may be a useful resource for determining the changes in the trend of imported systemic mycoses.

<https://doi.org/10.24171/j.phrp.2018.9.5.07>
pISSN 2210-9099 eISSN 2233-6052

©2018 Korea Centers for Disease Control and Prevention. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Imported systemic mycoses generally occurs amongst people that stay in an area where there is a high frequency of travel or business trips, and particularly in people who reside long-term in these areas such as archaeologists, speleologists, and immigrants [1-3]. Coccidioidomycosis, blastomycosis, histoplasmosis and paracoccidioidomycosis belong to imported

systemic mycoses. Coccidioidomycosis is a fungal infectious disease that occurs due to inhalation of arthroconidia of *Coccidioides* species where it mostly forms primary lesions in the lungs and disseminates to other areas. Most patients recover from these infections without treatment, but about 5% of patients with low immunity suffer a systemic infection in areas such as skin, bone, joint, and meninges with fatal results [4-6]. Blastomycosis occurs due to *Blastomyces dermatitidis*

*Corresponding author: Young-Kwon Kim

Department of Biomedical Laboratory Science, College of Medical Sciences, Konyang University, Daejeon, Korea

E-mail: ykkim3245@konyang.ac.kr

† Seung-Hak Cho and Young-Bin Yu contributed equally to the work.

‡ Young-Kwon Kim and Keun-Dol Yook contributed equally to the work.

©2018 Korea Centers for Disease Control and Prevention. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and has very diverse clinical symptoms. After primary lung infection it progresses into a systemic infection on the skin, in the urinary reproductive system, and the central nervous system [7]. Histoplasmosis occurs due to inflow of *Histoplasma capsulatum* and *H duboisii* spores into the respiratory system where it invades the alveoli [8]. Paracoccidioidomycosis is an imported systemic mycosis that occurs due to *Paracoccidioides brasiliensis* which disseminates into the lungs, lymph nodes, over the skin, and airways, and progression is acute [1].

Although imported systemic mycoses is a severe infectious disease with a high risk of death, there is a serious lack of overall epidemiological and clinical research about this disease. This disease is not registered as a national notifiable infectious disease which means there is no obligation to report the infection. It is estimated that there will be a continual increase in overseas travelers and an influx of immigrants that would increase the risk of dissemination of imported systemic mycoses. Therefore, this study was conducted to investigate the domestic occurrence of imported systemic mycoses and analyze the epidemiological characteristics to provide basic data for reference as a national notifiable infectious disease in the future.

Materials and Methods

1. Study design

Health insurance data between 2008 and 2012 were collected from the Health Insurance Corporation and analyzed for cases of coccidioidomycosis (KoICD, Korea International Classification of Diseases: B38), histoplasmosis (B39), blastomycosis (B40), and paracoccidioidomycosis (B41). The number of incidences were analyzed by considering medical records for 1 case if the case was duplicated within 2 months.

2. Epidemiological analysis

In order to determine the significance of imported systemic mycoses causing diseases, an epidemiological analysis of annual and regional prevalence and age- and gender-specific patterns of the prevalence for each imported systemic mycoses was performed. The annual prevalence of imported systemic mycoses was calculated, where patients with the disease who had been treated multiple times were counted as 1 case per year in the data analysis. The regional prevalence was calculated according to the locations of the medical institutions where the treatments had been provided.

3. Duration of hospitalization and cost analysis of therapy

The number of convalescence days of inpatients and outpatients for imported systemic mycoses were calculated

for the last 5 years. Medical care costs were calculated and classified as personal charges and insurance charges from the insurance items in the Health Insurance Corporation database. No insurance charge item was excluded from the medical care cost.

Results and Discussion

The frequency of imported systemic mycoses is continuously increasing which is threatening national health. This is thought to be due to an increase in overseas travelers visiting Korea and the population participating in more outdoor activities. Several cases of imported systemic mycoses have been reported in Korea [9-11]. This current study demonstrates fundamental epidemiological characteristics of imported systemic mycoses and medical treatments for these patients between the years of 2008 and 2012 in Korea.

1. Epidemiological characterization of imported systemic mycoses between 2008 and 2012 in Korea

A total of 1,148 infections with imported systemic mycoses were analyzed between 2008 and 2012. Approximately 229.6 cases occurred each year. Among the imported systemic mycoses, the prevalence of coccidioidomycosis (660 cases) was highest followed by histoplasmosis (245 cases), blastomycosis (171 cases), and lastly paracoccidioidomycosis (72 cases). Annual prevalence of imported systemic mycoses increased slowly from 0.49/100,000 persons in 2008, to 0.53/100,000 persons in 2012. The annual prevalence of coccidioidomycosis increased from 0.28/100,000 persons in 2008, to 0.36/100,000 persons in 2012, whereas the prevalence of other imported systemic mycoses was similar in each year or decreased (Table 1). The prevalence of coccidioidomycosis in females was higher than in males (Table 2). It was reported that female hormones and differences in genetic factors could affect coccidioidomycosis [12,13]. These studies also showed that progesterone and testosterone highly stimulated *Coccidioides* strains that cause infection. As shown in Table 3, age-specific patterns were observed in the imported systemic mycoses. By age group, there was a high rate of prevalence in people aged 0 to 9 years (0.71/100,000 persons) and in people aged 60 to 89 years (0.73/100,000 persons), whereas the prevalence rate was low in people aged 20 to 59 years. The prevalence rate of coccidioidomycosis was high in people aged 0 to 9 years and the prevalence of blastomycosis was high in people aged 60 to 89 years (Table 3). The regional prevalence is shown in Table 4. Gyeonggi (348 cases) and Seoul (219 cases) had the highest rates of infection, and Ulsan (10 cases) had the lowest rate of occurrence. The rate of infection according to region ranged from 0.18/100,000

Table 1. Prevalence rates of imported systemic mycoses by year.

Year	Population	No. of patients (per 100,000)									
		Systemic mycoses		Coccidioidomycosis		Histoplasmosis		Blastomycosis		Paracoccidioidomycosis	
2008	49,540,367	243	(0.49)	138	(0.28)	52	(0.10)	32	(0.06)	21	(0.04)
2009	49,773,145	191	(0.38)	98	(0.20)	50	(0.10)	30	(0.06)	13	(0.03)
2010	50,515,666	212	(0.42)	115	(0.23)	54	(0.11)	30	(0.06)	13	(0.03)
2011	50,734,284	234	(0.46)	126	(0.25)	45	(0.09)	44	(0.06)	19	(0.04)
2012	50,948,272	268	(0.53)	183	(0.36)	44	(0.09)	35	(0.07)	6	(0.01)
Total	251,511,734	1,148		660		245		171		72	

Data are presented as *n* (%).

Table 2. Prevalence rates of imported systemic mycoses by gender.

Gender	Population	No. of patients (per 100,000)									
		Systemic mycoses		Coccidioidomycosis		Histoplasmosis		Blastomycosis		Paracoccidioidomycosis	
Male	126,218,201	473	(0.38)	267	(0.21)	56	(0.04)	110	(0.09)	40	(0.03)
Female	125,293,533	675	(0.54)	393	(0.31)	189	(0.15)	60	(0.05)	32	(0.03)
Total	251,511,734	1,148		660		245		171		72	

Data are presented as *n* (%).

Table 3. Prevalence rates of imported systemic mycoses by age.

Age (y)	Population	No. of patients (per 100,000)									
		Systemic mycoses		Coccidioidomycosis		Histoplasmosis		Blastomycosis		Paracoccidioidomycosis	
0-9	24,121,916	172 (0.71)		114 (0.47)		38 (0.16)		13 (0.05)		7 (0.03)	
10-19	33,591,851	63 (0.19)		39 (0.12)		11 (0.03)		6 (0.02)		7 (0.02)	
20-29	34,475,220	102 (0.30)		62 (0.18)		28 (0.08)		8 (0.02)		4 (0.01)	
30-39	41,636,105	159 (0.36)		103 (0.25)		35 (0.08)		8 (0.02)		13 (0.03)	
40-49	43,928,536	206 (0.47)		118 (0.27)		44 (0.10)		28 (0.06)		16 (0.04)	
50-59	35,035,189	179 (0.51)		101 (0.29)		38 (0.11)		26 (0.07)		14 (0.04)	
60-69	20,749,025	133 (0.64)		63 (0.30)		26 (0.13)		40 (0.19)		4 (0.02)	
70-79	13,170,523	97 (0.74)		48 (0.36)		15 (0.11)		29 (0.22)		5 (0.04)	
80-89	4,227,934	34 (0.80)		10 (0.24)		9 (0.21)		13 (0.31)		2 (0.05)	
90-	575,435	3 (0.52)		2 (0.35)		1 (0.17)		0 (0.00)		0 (0.00)	
Total	251,511,734	1,148		660		245		171		72	

Data are presented as *n* (%).

persons in Ulsan to 0.59/100,000 persons in Gyeonggi. The reasons for the rate difference between the regions was not well understood. Further detailed epidemiological and clinical data are necessary to understand imported systemic mycoses

infection and immunity in the future.

The regional prevalence of coccidioidomycosis was similar across the country, with the range in incidences from 0.05/100,000 persons in Ulsan, to 0.44/100,000 persons in

Gyeonggi (Table 4). In the United States of America, about 150,000 patients have coccidioidomycosis every year [14]. Baddley et al [2] reported that the occurrence ratio of systemic mycosis within the USA was 46.1% for histoplasmosis, 44.5% for coccidioidomycosis, and 9.5% for blastomycosis. The average age of the patients were 75.7 years and 55% of these patients were male. Kirkland and Fierer [15] showed that the prevalence rate of coccidioidomycosis was highest in spring and late summer in Arizona, and in late summer and early fall in California. The highest rate of occurrence was reported in people that reside in semi-desert areas and in people who are involved in frequent outdoor leisure activities. Considering the 1-3 weeks incubation period of coccidioidomycosis, it was determined that the period of visiting a medical institution due to symptoms were similar. Furthermore, most of the investigation subjects had a history of temporarily residing or visiting the area during the spring and summer. However, a non-imported case of coccidioidomycosis was also reported [16]. In Japan, the prevalence rate of coccidioidomycosis has been rapidly increasing since the 1980s until recently. Fujio et al [17] reported that until 1998, 16 cases of coccidioidomycosis,

22 cases of histoplasmosis, 13 cases of paracoccidioidomycosis, and 1 case of *Penicilliosis marneffeii* were reported. However, 31 cases of coccidioidomycosis, 34 cases of histoplasmosis, 17 cases of paracoccidioidomycosis, and 1 case of *P marneffeii* were reported in 2005 [18]. Recently, the prevalence of imported systemic mycoses has increased in Japan [19].

2. Convalescence days and medical care charges according to different imported systemic mycoses

As shown in Table 5, amongst the 1,148 patients infected with imported systemic mycoses, inpatient treatment was 3.3% (38 cases), and 96.7% were treated as outpatients. Inpatient treatment of each coccidioidomycosis was 2.9% (19/660 persons), 4.1% (10/245 persons) of histoplasmosis, 3.5% (6/171 persons) of blastomycosis, and 4.2% (3/72 persons) of paracoccidioidomycosis. Total medical expense cost was 384.4 million won, with personal charges of 93.4 million won and insurance charges of 291 million won. Among the total expenses, hospitalization cost 272.7 million won and outpatient treatments cost 111.7 million won. About 86% (330.9 million won/384.4 million won) of the total expenses

Table 4. Prevalence rates of imported systemic mycoses by region.

Region	Population	No. of patients (per 100,000)				
		Systemic mycoses	Coccidioidomycosis	Histoplasmosis	Blastomycosis	Paracoccidioidomycosis
Gyeonggi	58,577,280	348 (0.59)	260 (0.44)	52 (0.09)	29 (0.05)	7 (0.01)
Seoul	51,173,741	219 (0.43)	101 (0.20)	69 (0.13)	38 (0.07)	11 (0.02)
Busan	17,772,034	59 (0.33)	27 (0.15)	17 (0.10)	9 (0.05)	6 (0.03)
Gyeongnam	16,401,116	92 (0.56)	38 (0.23)	14 (0.09)	9 (0.05)	31 (0.19)
Incheon	13,813,896	53 (0.38)	22 (0.16)	20 (0.14)	7 (0.05)	4 (0.03)
Gyeongbuk	13,438,345	35 (0.26)	17 (0.13)	7 (0.05)	8 (0.06)	3 (0.02)
Daegu	12,514,166	73 (0.58)	41 (0.33)	9 (0.07)	21 (0.17)	2 (0.02)
Chungnam	10,268,764	42 (0.41)	24 (0.23)	15 (0.15)	1 (0.01)	2 (0.02)
Jeonnam	9,581,516	56 (0.58)	40 (0.42)	11 (0.11)	4 (0.04)	1 (0.01)
Jeonbuk	9,333,685	35 (0.38)	17 (0.18)	6 (0.06)	10 (0.11)	2 (0.02)
Chungbuk	7,732,194	37 (0.48)	20 (0.26)	8 (0.10)	8 (0.10)	1 (0.01)
Gangwon	7,633,411	22 (0.29)	14 (0.18)	4 (0.05)	4 (0.05)	0 (0.00)
Daejeon	7,515,995	21 (0.28)	9 (0.12)	2 (0.03)	9 (0.12)	1 (0.01)
Gwangju	7,250,728	33 (0.46)	23 (0.32)	5 (0.07)	4 (0.06)	1 (0.01)
Ulsan	5,643,391	10 (0.18)	3 (0.05)	5 (0.09)	2 (0.04)	0 (0.00)
Jeju	2,861,472	13 (0.46)	4 (0.14)	1 (0.04)	8 (0.28)	0 (0.00)
Total	251,511,734	1,148	660	245	171	72

Data are presented as n (%).

Table 5. Medical costs of imported systemic mycoses in Korea.

		No. of patients	Self-cost (Korean won)	Insurance cost (Korean won)	Total cost (Korean won)
Systemic mycosis	Inpatient	38	61,757,950	210,985,310	272,743,260
	Outpatient	1,110	31,680,200	80,102,530	111,782,730
Coccidioidomycosis	Inpatient	19	56,691,790	190,083,600	246,775,390
	Outpatient	641	22,511,660	61,636,340	84,148,000
Histoplasmosis	Inpatient	10	1,767,940	8,922,980	10,690,920
	Outpatient	235	4,782,740	7,085,050	11,867,790
Blastomycosis	Inpatient	6	3,072,960	9,336,910	12,409,870
	Outpatient	165	2,354,140	5,113,340	7,467,480
Paracoccidioidomycosis	Inpatient	3	225,260	2,641,820	2,867,080
	Outpatient	69	2,031,660	6,267,800	8,299,460

were used for the treatment of coccidioidomycosis. The treatment cost for coccidioidomycosis from 2008 to 2012 was 330.9 million won, with personal charges of 79.2 million won and insurance charges of 251.7 million won. Most of the expenses for the coccidioidomycosis treatment was for inpatient treatment (Table 4).

Due to frequent travels abroad, imported systemic mycoses may increase in the future in Korea. Therefore, development of diagnosis and therapy against imported systemic mycoses, especially coccidioidomycosis, is necessary. Increase of eosinophil numbers in the blood can be seen in various disease groups, suggesting that this may be an important marker for disease in diverse cases in endemic disease areas. Therefore, increased eosinophil counts in peripheral blood tests and bronchial biopsy with a medical history of traveling to endemic disease areas can be leading evidence in suspecting imported systemic mycoses infection [20,21]. However, it is not possible to diagnose coccidioidomycosis just with elevated eosinophil counts because eosinophilia is a common outcome of allergies, infectious disease, and medication. For early diagnosis of imported systemic mycoses, the following observations are recommended; i) Nodular erythema, skin lesions such as erythema multiforme, ii) fever spanning over 2 weeks, fatigue, joint pain, iii) unexplainable peripheral blood eosinophilia, iv) presence of respiratory symptoms, 1 or more cases of hospital care, chest x-ray imaging, presence of specific symptoms or prognosis e.g. diagnosed with antibiotics, v) history of travel to endemic disease areas such as the USA, then imported systemic mycoses should be suspected.

Outbreaks of coccidioidomycosis in the future are highly

possible therefore, diagnosis standards for imported systemic mycoses need to be established with a matter of urgency. The data in this study may be a useful resource for determining changes in the trends of imported systemic mycoses.

Conflicts of Interest

No potential conflicts of interest relevant to this article was reported.

Acknowledgments

This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (fund code# 2013-E2400200).

References

- [1] Bonifaz A, Vázquez-González D, Perusquía-Ortiz AM. Endemic systemic mycoses: coccidioidomycosis, histoplasmosis, paracoccidioidomycosis and blastomycosis. *J Dtsch Dermatol Ges* 2011;9(9):705-14.
- [2] Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis* 2011;17(9):1664-9.
- [3] Panackal AA, Hajjeh RA, Cetron MS, et al. Fungal infections among returning travelers. *Clin Infect Dis* 2002;35(9):1088-95.
- [4] Park DJ, Jang YH, Lee SJ, et al. A case of coccidioidomycosis showing cutaneous and pulmonary nodules. *Kor J Med Mycol* 2004;9(3):190-5.
- [5] Szeyko LA, Taljanovic MS, Dzioba RB, et al. Vertebral coccidioidomycosis: presentation and multidisciplinary management. *Am J Med* 2012;125(3):304-14.

- [6] Kirkland TN, Fierer J. Coccidioidomycosis: a reemerging infectious disease. *Emerg Infect Dis* 1996;2(3):192-9.
- [7] Cho JH, Suh JS, Kim JH. Systemic blastomycosis with osseous involvement of the foot: A case report. *J Korean Foot Ankle Soc* 2005;9(2):216-9. [in Korean].
- [8] Jeong HW, Sohn JW, Kim MJ, et al. Disseminated histoplasmosis and tuberculosis in a patient with HIV infection. *Yonsei Med J* 2007;48(3):531-4.
- [9] Chang SH, Shim SH, Kwak JE, et al. A case report of cutaneous coccidioidomycosis. *Korean J Pathol* 2008;42(4):223-5. [in Korean].
- [10] Jhun BW, Kim DM, Park JH, et al. A case of pulmonary blastomycosis mimicking pulmonary tuberculosis. *Tuberc Respir Dis* 2012;72(1):77-81.
- [11] Seo CG, Seo YW, Park HP, et al. A case of blastomycosis after traveling around non-imported area. *Tuberc Respir Dis* 2005;58(6):619-23.
- [12] Drutz DJ, Huppert M, Sun SH, et al. Human sex hormones stimulate the growth and maturation of *Coccidioides immitis*. *Infect Immun* 1981;32(2):897-907.
- [13] Louie L, Ng S, Hajjeh R, et al. Influence of host genetics on the severity of coccidioidomycosis. *Emerg Infect Dis* 1999;5(5):672-80.
- [14] Centers for Disease Control and Prevention (CDC). Increase in Coccidioidomycosis- California, 2000-2007. *MMWR Morb Mortal Wkly Rep* 2009;58(5):105-9.
- [15] Kirkland TN, Fierer J. Coccidioidomycosis: a reemerging infectious disease. *Emerg Infect Dis* 1996;2(3):192-9.
- [16] Desai SA, Minai OA, Gordon SM, et al. Coccidioidomycosis in non-imported areas: a case series. *Respir Med* 2001;95(4):305-9.
- [17] Fujio J, Nishimura K, Miyaji M. Epidemiological survey of the imported mycoses in Japan. *Jpn J Med Mycol* 1999;40(2):103-9.
- [18] Kamei K. Imported mycoses in Japan: their present status and problems. *Jpn J Med Mycol* 2005;46(1):17-20.
- [19] National Institute of Infectious Diseases. *Mycoses in Japan as of 2012*. Byogen Biseibutsu Kenshutsu Joho Geppo 2013;34(1):1-2.
- [20] Kawabata M, Homma S, Sakamoto S, et al. A case of pulmonary coccidioidomycosis presented with bilateral infiltrative opacities and eosinophilia. *Kansenshogaku Zasshi* 2004;78(6):514-8.
- [21] Koepke A, Albus C, Barth A, et al. Coccidioidomycosis: differential diagnosis of lung infiltrates with peripheral eosinophilia. *Dtsch Med Wochenschr* 1989;114(6):218-21.