Epidemiological Characterization of Imported Systemic Mycoses Occurred in Korea

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ABSTRACT

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.

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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.
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.
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

| 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 (%).

| 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 (%).

| 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 (%).
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 marneffei were reported. However, 31 cases of coccidioidomycosis, 34 cases of histoplasmosis, 17 cases of paracoccidioidomycosis, and 1 case of P. marneffei 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.

| 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 (%).
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.

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