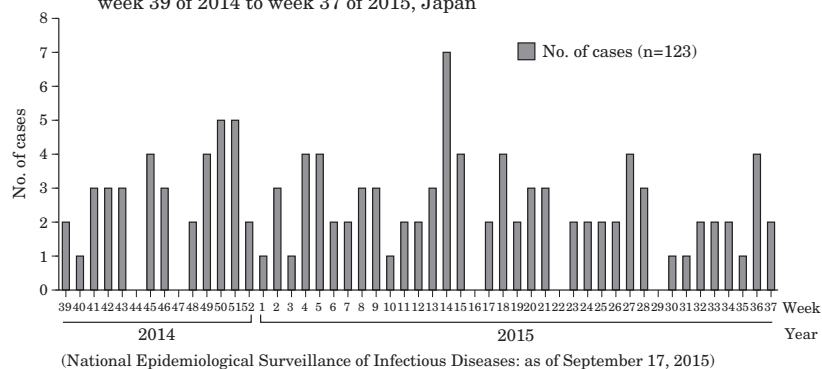


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## &lt;THE TOPIC OF THIS MONTH&gt;

## Disseminated cryptococcal infection in Japan (2014 Week 39–2015 Week 37)

Figure 1. Weekly number of reported disseminated cryptococcal infection cases, week 39 of 2014 to week 37 of 2015, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 17, 2015)

Cryptococcal infection is caused by infection of a fungi belonging to the genus *Cryptococcus*, usually present in the soil or other environments. The route of infection is inhalation or via a skin injury. No person-to-person infection has been reported. Infections spreading systemically and/or to the central nervous system (CNS) are classified as disseminated cryptococcal infection (see p. 185 of this issue).

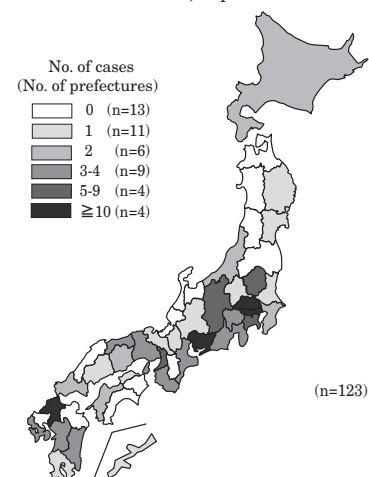
Disseminated cryptococcal infection is a category V infectious disease under the Infectious Diseases Control Law. All cases shall be notified within 7 days after the diagnosis. The notification criteria, including detection of *Cryptococcus* in the cerebrospinal fluids, blood or otherwise sterile clinical specimens and/or presence of *Cryptococcus* capsular antigen in the cerebrospinal fluids, are found in <http://www.nih.go.jp/niid/images/iasr/36/428/de4281.pdf>.

Although disseminated cryptococcal infection can occur among otherwise healthy persons, risk factors include diabetes, malignant tumors, hematological diseases, renal diseases, collagen diseases, HIV infection, and use of steroid and other immunosuppressants. Factors that lead to systemic infection or the mechanism of the pathogen's high affinity to CNS have not been well elucidated. Antifungal chemotherapy is used for treatment, but often requires a long period of time, even for healthy persons (see p. 191 of this issue).

Fungi belonging to the genus *Cryptococcus* have a thick capsule. There are two species, *C. neoformans* and *C. gattii*, which are differentiated genetically. *C. neoformans* is distributed worldwide and grows in bird droppings. *C. gattii* is localized in tropical and subtropical regions such as Australia, and detected from trees such as *Eucalyptus camaldulensis*. Compared with *C. neoformans*, *C. gattii* infections tend to be more severe and occur more frequently among otherwise healthy persons (see pp. 186 & 191 of this issue).

In Japan, *C. neoformans* infection cases have been reported frequently. While *C. gattii* infections, associated with high case fatality and linked to environmentally-derived regional clusters, have been reported in recent years from North America (see p. 186 of this issue), environmental *C. gattii* colonization has not been reported in Japan. However, with the report of a *C. gattii* infection case with no known travel history to an endemic region and no known suspected infection source (see p. 187 of this issue), disseminated cryptococcal infection was added as a notifiable category V infectious disease, under the Infectious Diseases Control Law on 19 September 2014; the aim was to facilitate epidemiological investigation of cryptococcal infections, including those caused by *C. gattii*.

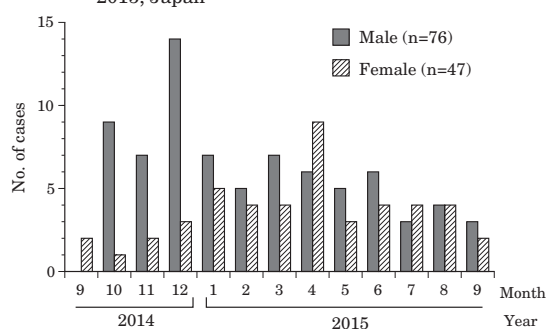
Figure 2. Reported number of disseminated cryptococcal infection cases, by prefecture, week 39 of 2014 to week 37 of 2015, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 17, 2015)

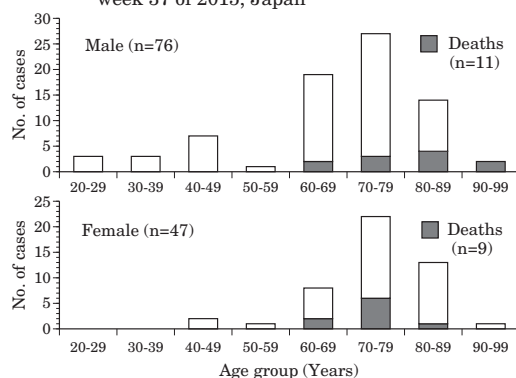
(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Monthly number of reported disseminated cryptococcal infection cases by gender, September 2014-September 2015, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 17, 2015)

Figure 4. Age distribution of disseminated cryptococcal infection cases by gender, week 39 of 2014 to week 37 of 2015, Japan



(National Epidemiological Surveillance of Infectious Diseases: as of September 17, 2015)

Table. Clinical signs and symptoms of disseminated cryptococcal infection cases reported, as recorded on the notification form

Clinical signs and symptoms	Total (n=123)	Immune competent (n=18)	Immunocompromised (n=105)
Fever	74 (60%)	9 (50%)	65 (62%)
Disturbance of consciousness	53 (43%)	10 (56%)	43 (41%)
Fungemia	47 (38%)	4 (22%)	43 (41%)
Headache	37 (30%)	8 (44%)	29 (28%)
Respiratory symptom	30 (24%)	5 (28%)	25 (24%)
Abnormal chest roentgenogram	25 (20%)	3 (17%)	22 (21%)
Stiff neck	16 (13%)	3 (17%)	13 (12%)
Central nervous system lesion	13 (11%)	3 (17%)	10 (10%)
Rash	11 ( 9%)	—	11 (10%)
Convulsion	5 ( 4%)	3 (17%)	2 ( 2%)
Paralysis	1 ( 1%)	—	1 ( 1%)
Erythema	1 ( 1%)	—	1 ( 1%)
Endophthalmitis	—	—	—
Bone lesion	—	—	—
Other	11 ( 9%)	1 ( 6%)	10 (10%)

(National Epidemiological Surveillance of Infectious Diseases: as of September 17, 2015)

### National Epidemiological Surveillance of Infectious Diseases (NESID)

From week 39 of 2014 when disseminated cryptococcal infection became a category V infectious disease till week 37 of 2015, 123 cases were reported from 34 of the 47 prefectures (prefectures with the largest number of reported cases were Tokyo 12; Saitama 11; Aichi 10; Fukuoka 10; Kanagawa 9; Nagano 7; Osaka 7; Tochigi 5) (as of 17 September 2015) (Fig. 1 & Fig. 2). The reported annual incidence per 1,000,000 population was 0.97 (prefectures with the highest reported annual incidence were Tottori 6.97; Yamanashi 3.57; Nagano 3.32; Wakayama 3.09; Miyazaki 2.69; Tochigi 2.53; Nagasaki 2.16; Fukuoka 1.96). No seasonality was observed for disseminated cryptococcal infections (Fig. 3).

#### Sex and age distribution:

Among the 123 cases, 76 were male and 47 were female (male to female ratio: 1.6). The median age was 74 years (range: 20-99 years). Cases 60 years or older (106 cases) occupied 86% of all cases (82% among male cases and 94% among female cases) (Fig. 4). Twenty cases (16%; 11 males and 9 females) had died at the time of notification; the median age was 77 years (range: 60-91 years).

**Suspected infection route and underlying health conditions:** Among the 123 cases, 105 cases (85%), consisting of 68 males (89% of male cases) and 37 females (79% of female cases), had underlying conditions or were immunocompromised. Twelve cases (10%) (8 males; 4 females) had history of contact with the feces of birds such as pigeon or chicken. Thirteen cases had no known risk factors. Seven cases had more than one suspected risk factor listed. Though cryptococcal infection is an indicator of AIDS, there were only 8 cryptococcal infection cases with HIV/AIDS (all males; age 31-50 years) (see pp. 188 & 189 of this issue).

**Clinical picture:** The table lists the reported cases' clinical signs and symptoms, as recorded on the notification form. Sixty percent of the cases had fever. Other reported clinical signs and symptoms included disturbance of consciousness, fungemia, central nervous system lesion, respiratory symptoms, abnormal chest roentgenogram, etc.

**Laboratory diagnosis:** Among the 123 cases, 108 cases (88%) were diagnosed by detection of *Cryptococcus* in blood and/or cerebrospinal fluid specimens, 63 cases (51%) by detection of *Cryptococcus* capsular antigen by latex agglutination, and 34 cases (28%) by histological and cytological detection of encapsulated yeast cells in cerebrospinal fluid (some cases were diagnosed by more than one method). Under the current surveillance system, the respective proportion of infections caused by *C. neoformans* and *C. gattii* is unknown.

#### Summary

Japan has so far not experienced a cluster of epidemiologically-linked cryptococcal infection cases. The newly established surveillance system under NESID will further elucidate the epidemiology and the clinical picture of disseminated cryptococcal infections in Japan. It is hoped that potential risk factors may be identified, preventive measures may be developed, and early outbreak detection and intervention strategies may be established.

Latency of *Cryptococcus* ranges from several months to several years. As cryptococcal infection may become serious even among otherwise healthy persons, it is critically important that clinicians suspect cryptococcal infections at an early stage, while differentiating it from other fungal infections such as *Coccidioides* (IASR 34: 1-2, 2013) (see p. 192 of this issue). As cryptococcal infection treatment may occasionally fail, development of vaccines and new therapeutics are needed.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.