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Emergence of *Cryptococcus gattii* in a Novel Environment Provides Clues to Its Incubation Period

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Cryptococcus gattii **emerged in 1999 in a distinct ecologic environment on Vancouver Island, Canada. Estimates of incubation period were derived from an analysis of travelers with discreet exposures to this region. Individual case incubation periods ranged from 2 to 11 months, with a median of 6 to 7 months.**

The incubation periods of many fungal diseases remain uncharacterized owing largely to ill-defined exposures. A fungal pathogen, *Cryptococcus gattii* causes respiratory and disseminated infections that affect predominantly immunocompetent individuals. Its incubation period is currently unknown (5). *C. gattii* was historically thought to be limited to the tropics and subtropics; its most common environmental reservoirs included eucalypts and other tropical tree species not found in Canada (9). Between 1999, when the fungus first emerged on Vancouver Island, Canada, and the end of 2004, *C. gattii* has affected over 100 individuals; all cases either lived within a single biogeoclimatic zone on Vancouver Island or lived off-island but had traveled to this zone in the recent past. Environmental investigations during this period isolated the organism from trees native to this zone while sampling in off-island environments failed to find evidence of the fungus (1, 8). The specific time of exposure could not be determined for individuals living within this biogeoclimatic zone as the fungus was found to be ubiquitous in this environment. However, the focal emergence of *C. gatii* allows for a crude estimate of incubation period to be calculated based on travelers with discrete exposures to this region of endemicity.

Cases were British Columbia residents with culture-confirmed *C. gattii* serotype B infections identified between 1 January 1999 and 31 December 2004 who did not reside on Vancouver Island. As *Cryptococcus* infections were not reportable in British Columbia until June 2003, cases were identified by a retrospective search of the provincial hospital separations database, a review of *Cryptococcus* isolates stored at the provincial reference laboratory, and prospective identification by medical microbiologists. Isolates were serotyped using Crypto-Check (Iatron Laboratories, Tokyo, Japan), a commercially available agglutination test. All cases had molecular types compatible with *C. gattii* exposure on Vancouver Island (VGIIa and VGIIb) (8).

Cases were interviewed by phone and asked to provide exact onset dates when possible or to estimate onset to the nearest month and year. If cases were asymptomatic, the date of initial presentation to medical services was used as a proxy; this was extracted from enhanced surveillance reports completed by the case's physician. Cases were interviewed about travel in the 12-month period prior to onset; date(s) of travel to Vancouver Island were estimated to the closest month and year. Incubation period was calculated as the date of onset minus the date of travel to Vancouver Island. When exact dates were unavailable, estimates were rounded to the first day of the month. In the event that more than one trip to Vancouver Island was made, incubation periods were calculated for each visit.

Thirteen off-island culture-confirmed cases were identified. Four cases were lost to follow-up, and two were excluded as the timing of their onset or travel was unclear. Of the remaining seven, the earliest case reported symptom onset in August 2000. All cases reported taking short trips to Vancouver Island, ranging from 1 to 7 days. Three cases experienced pulmonary disease only, one presented with both pulmonary disease and cryptococcal meningitis, and one presented with cryptococcal meningitis and skin lesions; two cases had pulmonary infections characterized by pulmonary nodules on chest X ray, but no reported symptoms at the time of the X ray. Individual incubation periods ranged from 2 to 11 months (Table 1). Two individuals had traveled to Vancouver Island twice in the year before disease onset. The median incubation period for all cases was therefore calculated twice, once assuming the longest incubation period for these two individuals (7.47 months) and again assuming the shortest (6.32 months).

Because in many cases exact dates were unavailable, the incubation periods presented here represent estimates only. Rounding errors may have over- or underestimated the true incubation period by as much as 1 month. The date of initial presentation was used as a proxy for onset date in two patients with pulmonary nodules on X ray but no reported symptoms at the time of diagnosis. These two patients were treated for their infection, and inclusion of their incubation periods may have over- or underestimated the median value depending on when during the natural course of disease their infections were discovered. Besides travel to Vancouver Island, two patients had traveled to other areas known to be endemic for *C. gattii* within a year of diagnosis—Spain and California. While fungal acquisition in these areas cannot be completely ruled out, a review of the published literature indicates that VGII molecular types have not been previously reported from Spain (3, 6). The

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TABLE 1. Incubation period of *C. gattii* calculated for culture-confirmed cases identified 1 January 1999 to 31 December 2004[a]

Case no.	Sex[b]	Age (yr)	Onset date (mo/day/yr)	Date of travel to Vancouver Island	Incubation period		Presentation[c]
					Days	Mo	
1	F	64	8/24/2000	October 1999	328	10.79	
				March 2000	176	5.79	CNS, skin lesion
2	M	73	3/01/2001*	June 2000	273	8.98	Pulmonary—asymptomatic*
3	M	60	November 2001†	September 2001	61	2.01	Pulmonary
4	M	57	5/14/2004*	July 2003	318	10.46	Pulmonary—asymptomatic*
5	M	55	1/31/2002	September 2001	152	5.00	Pulmonary
6	M	12	January 2002†	July 2001	184	6.05	Pulmonary
				October 2001	92	3.00	
7	F	21	July 2003†	October 2002	273	8.98	CNS, pulmonary

[a] *, asymptomatic pulmonary cases with positive chest X ray (onset date estimated by date of initial presentation to medical services); †, estimated dates rounded to the 1st of the month.
[b] F, female; M, male.
[c] CNS, central nervous system disease characterized by meningitis.

traveler to California was diagnosed within weeks of returning, which, if acquisition had occurred there, represents an unusually shorter incubation period than described for other cases exposed to Vancouver Island.

Despite these limitations, these data constitute the first quantitative estimates of the incubation period of *C. gattii* derived from a common source exposure. Single case reports in individuals returning from different areas of endemicity have been published previously. The first observation of *C. gattii* in the United Kingdom was in a patient who had returned from a 4-year stay in South Africa only 5 days before presentation, effectively blurring the period of exposure and any calculation of incubation period (2). A patient with *C. gattii* serotype B diagnosed in New York City in 1984 had traveled to known areas of endemicity 4 (Mexico), 5 (Mexico), and 13 (California) years prior to onset (4). As this case suggests, the incubation period for *C. gattii* may sometimes be longer; however, travel to areas not known to be endemic at the time may also have been responsible for illness in this individual. A more recent case report of a Japanese traveler to Australia estimates 1 month between the date of arrival at the area of endemicity and presentation to hospital (10), slightly less than the shortest incubation period presented here for travelers to Vancouver Island. Even among individuals exposed to Vancouver Island, considerable variation in the length of incubation period exists and this may reflect differences in host factors, exposure dose, or variation in recognition of symptom onset.

While typically longer than most bacterial and viral infections, other fungal diseases of the lower respiratory system such as histoplasmosis and coccidioidomycosis have much shorter incubation periods than the 6 to 7 months described here for *C. gattii*. Symptoms of histoplasmosis typically appear within 3 to 17 days of exposure, while the incubation period for primary infection with *Coccidioides immitis* is 1 to 4 weeks (5). On the other extreme, estimates of incubation period for *Cryptococcus neoformans* var. *grubii* are much longer than those for *C. gattii*. Garcia-Hermoso et al. describe symptom development in individuals who had been living outside the geographic region most compatible with their molecular strain profile for a median of 110 months, supporting the idea of a dormant phase followed by later activation of the fungus (7). The much shorter 6- to 7-month incubation period demonstrated here for *C. gattii* is more consistent with primary infection.

We have taken advantage of the unique epidemiology of this outbreak, characterized by the emergence of a new disease in a well-defined environment, to provide an estimate of the incubation period for *C. gattii*. An understanding of the length of the incubation period is critical to the ability to track the spread of this disease. Detection of disease in people with no travel to areas of endemicity within a year of symptom onset may signal the emergence of the fungus in a new environment.

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REFERENCES

1. **Bartlett, K. H., L. MacDougall, S. Mak, C. Duncan, S. Kidd, and M. Fyfe.** 2004. Abstr. 16th Biometeorol. Aerobiol. Meet., abstr. 5.5. [Online.] http://ams.confex.com/ams/pdfpapers/80027.pdf.
2. **Bodasing, N., R. A. Seaton, G. S. Shankland, and D. Kennedy.** 2004. *Cryptococcus neoformans var. gattii* meningitis in an HIV-positive patient: first observation in the United Kingdom. J. Infect. **49:**253–255.
3. **Boekhout, T., B. Theelen, M. Diaz, et al.** 2001. Hybrid genotypes in the pathologenic yeast Cryptococcus neoformans. Microbiology **147:**891–907.
4. **Bottone, E. J., P. A. Kirschner, and I. F. Salkin.** 1986. Isolation of highly encapsulated *Cryptococcus neoformans* serotype B from a patient in New York City. J. Clin. Microbiol. **23:**186–188.
5. **Chin, J. (ed.).** 2000. Control of communicable diseases manual, 17th ed. American Public Health Association, Washington, D.C.
6. **Colom, M. F., S. Frasés, C. Ferrer, et al.** 2005. First case of human Cryptococcosis due to *Cryptococcus neoformans var. gattii* in Spain. J. Clinical Microbiology **43:**3548–3550.
7. **Garcia-Hermoso, D., G. Janbon, and F. Dromer.** 1999. Epidemiological evidence for dormant *Cryptococcus neoformans* infection. J. Clin. Microbiol. **37:**3204–3209.
8. **Kidd, S. E., F. Hagen, R. L. Tscharke, M. Huynh, K. H. Bartlett, M. Fyfe, L. MacDougall, T. Boekhout, K. J. Kwon-Chung, and W. Meyer.** 2004. A rare genotype of *Cryptococcus gattii* caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada). Proc. Natl. Acad. Sci. USA **101:** 17258–17263.
9. **Sorrell, T. C.** 2001. *Cryptococcus neoformans* variety *gattii*. Med. Mycol. **39:**155–168.
10. **Tsunemi, T., K. Tomoyuki, Y. Fumimura, et al.** 2001. Immunohistochemical diagnosis of Cryptococcus neoformans var. gattii infection in chronic meningoencephalitis: the first case in Japan. Int. Med. **40:**1241–1244.