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Title: Serious fungal infections in Canada

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Abstract

There are currently no nationwide epidemiological data on fungal infections in Canada. We estimated the burden of serious fungal diseases using literature review and modelling, as per a methodology previously described by the LIFE program (www.LIFE-worldwide.org). Among the population of Canada (35.5 million in 2014), it was estimated that approximately 1.8% are affected by a serious fungal infection. Recurrent vulvovaginal candidiasis, severe asthma with fungal sensitization and allergic broncho-pulmonary aspergillosis are the most frequent infections with a population prevalence of 498,688 (1,403/100,000), 73,344 (206/100,000) and 61,854 (174/100,000) cases, respectively. Over 3,000 invasive fungal infections are estimated to occur annually, with an incidence of 2,068 cases (5.8/100,000) of invasive candidiasis, 566 cases (1.6/100,000) of invasive aspergillosis, 252 cases (0.69/100,000) of *Pneumocystis* pneumonia, 99 cases (0.28/100,000) of endemic mycoses and 63 cases (0.18/100,000) of cryptococcosis. These estimates warrant validation through more formal epidemiological studies in Canada.

Key words: fungal diseases, burden, epidemiology, Canada

1 **Introduction**

2
3 Canada is a high-income country with a gross domestic product of 1,551 billion dollars (USD)
4 in 2015 (GDP per capita, 43,249). Several studies have examined the epidemiology of fungal
5 infections in Canada, but most were local (single-centered, regional or provincial) and focused
6 on individual infections in specific populations. A single study reported on the burden of
7 invasive fungal infections at the national level, however these data are over 20-years-old [1],
8 and relied largely on clinical microbiology laboratory records review. Since that time, the
9 Canadian population has expanded by 26%; use of immunosuppressive therapies that increase
10 the risk of fungal infection have risen in importance, e.g. solid organ and stem cell
11 transplantation and immunosuppressive biologic therapies; fungal diagnostics have improved;
12 and medical care practices have evolved greatly. Hence, we sought to provide an estimate of
13 the national burden of serious fungal infections.

15 **Material and methods**

16 The current study targeted serious fungal infections, which were defined as fungal-associated
17 syndromes (infection or hypersensitivity) causing significant morbidity or mortality. The
18 LIFE methodology (www.life-worldwide.org) was followed as described previously [2,3],
19 with some modifications.

20
21 In brief, an annual burden was estimated for each targeted serious fungal disease and
22 presented as: i) absolute number of cases per year in Canada (representing either incident or
23 prevalent cases depending on the nature of the infection), and ii) annual rates (incidence or
24 prevalence), using the annual number of cases as the numerator and the entire Canadian
25 population as the denominator. For simplicity, the 2014 Canadian population (n=35,540,419

[4]) was used regardless of the year from which the numerator data originated. To calculate the absolute number of cases per year in Canada, data derived from various sources were aggregated in a step-wise hierarchic fashion, starting with notifiable fungal diseases obtained directly from national and provincial public health agencies, followed by local data from individual centers or health authorities cited in peer review or grey literature and extrapolated to the total Canadian population (with the exception of geographically-confined infections, *Cryptococcus gattii* and endemic mycoses) and finally extrapolations from other countries' estimates.

Sources included: Statistics Canada (total and adult female population [4], asthma prevalence [5]), the Canadian Cancer Society (acute leukemia [6] and overall cancer incidence [7]), the Canadian Institute for Health Information (number of solid organ transplants) [8], the Canadian Bone Marrow Transplantation Group (number of hematopoietic stem cell transplants), the Organization for Economic Co-operation and Development (number of chronic obstructive pulmonary disease [COPD] admissions) [9], the Public Health Agency of Canada (HIV prevalence and AIDS incidence) [10], the World Health Organization (pulmonary tuberculosis incidence) [11] and Cystic Fibrosis Canada (cystic fibrosis prevalence) [12]. Of note, AIDS cases from the province of Québec are not currently reported to the Public Health Agency of Canada, so the number was calculated at pro rata of Québec population, assuming the same incidence as the rest of the country.

A map showing the geographic distribution of endemic mycoses was created using SmartDraw (SmartDraw Software, LLC, San Diego, CA, USA).

Results and Discussion

Estimated annual numbers of cases of serious fungal diseases and the corresponding population rates are summarized in Table 1. The distribution of geographically-confined mycoses is shown in Figure 1.

Opportunistic invasive fungal infections

The burden of invasive candidiasis (IC) was extrapolated from data reported from the Calgary health region and the Province of Québec [13,14]. In the first study, candidemia incidence was estimated at 2.8 cases per 100,000 person-year over a 5-year period, based on blood and cerebrospinal fluid culture (approximately 93% of cases were candidemia). Of note, incidence was significantly higher (3.7/100,000) during the latter 3 years of the study. In the second study, the reported annual incidence of candidemia was 3 cases per 100,000 population, with 50% of cases arising from intensive care units. These rates translate to at least 1,034 cases of candidemia each year in Canada. Deep-seated *Candida* infections such as peritonitis and endophthalmitis are accompanied by positive blood cultures in at most 50% of cases [15]. This observation is consistent with a recent nationwide German study which reported that the incidence of IC without candidemia was the same as candidemia [3]. Applying this ratio, a total of 2,068 IC cases are estimated to occur annually in Canada.

Invasive aspergillosis (IA) was largely reported in the main high-risk populations including patients with hematologic malignancies, hematopoietic stem cell transplant (HSCT) recipients and solid-organ transplant recipients (SOT), as well as patients with severe chronic obstructive pulmonary disease (COPD). A recent study from a Montreal center found an incidence of 8.9% among adult acute leukemia patients (both myelogeneous [AML] and

lymphocytic [ALL]) [16], consistent with other international reports [17]. There were 1,215 cases of AML in Canada in 2010 [6], corresponding to approximately 108 cases of IA that year. Since AML and ALL were reported to account for approximately 75% of IA cases occurring among patients with hematologic malignancies [18], an additional 36 IA cases are estimated to occur in patients with other hematologic malignancies. The incidence of IA amongst patients undergoing SOT was estimated using data from a prospective North American cohort study of these populations (12-month cumulative incidence: kidney, 0.2%; liver, 0.5%; lung, 3.8%; heart, 0.8%; pancreas, 0.2%) [19]. The incidence of IA after allogeneic HSCT was estimated at 7.5% based on recent observational and interventional studies [20-23]. In 2012, there were 1,358, 494, 194, 164 and 77 kidney, liver, lung, heart and pancreas transplants in Canada, respectively [8], corresponding to an estimated 14 cases of IA. A total of 1,200 allogeneic HSCT are performed annually in Canada (personal communication, Canadian Bone Marrow Transplantation Group), resulting in an additional estimated 90 cases of IA per year. Of note, large prospective cohort studies found that least 20% of IA cases occur more than a year after SOT and HSCT [24,19], representing an additional 26 cases. In addition, data from the North American Path Alliance registry showed that 22.3% of IA cases were associated with other underlying diseases, including solid tumors, HIV/AIDS and autologous HSCT, which translates to 78 cases. Hence, 352 IA cases are estimated to occur annually amongst traditional immunocompromised populations. Finally, 59,514 hospital admissions for chronic obstructive pulmonary disease (COPD) [9] account for approximately 214 IA cases, or 3.6 cases per 1,000 admissions [25], resulting in a total of 566 IA cases annually.

Over a 10-year period (2003-2012), 264 cases of *Pneumocystis pneumonia* (PCP) were diagnosed in single tertiary care centre in Montreal (personal communication, Dr M. Laskine,

Centre Hospitalier de l'Université de Montréal). Using this center's estimated catchment population of 3.4 million (41% of Quebec's population), one might expect as many as 252 cases per year across Canada.

A *C. gattii* outbreak has been ongoing in the province of British Columbia since 1999 [26] (Figure 1). Between 2010 and 2013, a mean of 23 *C. gattii* infections per year were reported to the British Columbia CDC [27]. During a 2-year period (1992-1994) prior to the *C. gattii* outbreak, investigators had identified 81 cases of *C. neoformans* disease across the country [1]. Assuming that *C. gattii* infections represent an increased burden of disease and that *C. neoformans* infection rates remain unchanged, then at least 63 cryptococcal infections are estimated to occur annually.

Endemic mycoses

Blastomycosis is endemic in the provinces of Ontario, Québec and Manitoba (Figure 1). It is considered hyperendemic in an area of northwestern Ontario [28]. In the former two provinces, recently published reports suggest that a mean of 44 culture-proven cases occur annually, [29,30]. In Manitoba where blastomycosis is a reportable infection, 19 cases were documented in 2013 [31]. Collectively, these data suggest an annual incidence of at least 63 cases of blastomycosis in these three provinces, hence in Canada.

Histoplasmosis occurs mainly along the Saint-Lawrence river valley, in Ontario and Québec (Figure 1). Histoplasmin reactivity studies have shown a prevalence of 9-27% in southern Québec [32-34]. The incidence of active histoplasmosis has been estimated at 27 cases per year in Canada in a study spanning the 2-year period 1992-1994 [1].

Coccidioides immitis/posadasii is not indigenous in Canada, though cases of active coccidioidomycosis are imported. Studies have estimated there are between 2 and 9 cases of coccidioidomycosis annually, largely in returning travelers [35,1].

Non-invasive pulmonary aspergillosis

Extrapolating from pulmonary tuberculosis 2014 annual incidence data (n=1,065) [11], the prevalence of cases of CPA following tuberculosis were estimated at 148 cases using a previously reported model [36]. If prior pulmonary tuberculosis is the predisposing factor in approximately 30% of cases of CPA [37], an estimated 492 new cases of CPA are expected.

ABPA burden was derived from the number of Canadian adults with asthma (n=2,444,804) [5] and the number of patients suffering from cystic fibrosis (CF; n=4,077) [12]. The proportion of ABPA among asthma patients was estimated at 2.5% [38] and 18% in those with CF [39], leading to a calculated national prevalence of 61,854 cases of ABPA. SAFS burden was derived from asthma prevalence and estimated at 73,344 cases, assuming a severe asthma prevalence of 10% of all cases of asthma and an *Aspergillus* sensitization prevalence of 30% [40].

Mucosal candidiasis

RVVC is reported to affect up to 9% of women of reproductive age [41]. Canadian prevalence of RVVC was calculated by applying 6% to the Canadian adult women's population (between 15 and 50 years old; n=8,311,477 [4]), yielding an estimated 498,688 cases present.

1
2 In a systematic review, the prevalence of OC in cancer patients was estimated 7.5%, 39.1%
3 and 32.6%, before, during and after the end of treatment, respectively [42]. In Canada,
4 196,900 new cases of cancer were estimated in 2015 [7]. Because the total number of patients
5 undergoing treatment and the survival rates are not known, only pre-treatment OC was
6 considered and the estimated prevalence was calculated at 14,767 cases of OC nationally.
7 HIV infection is responsible for an additional 752 cases, including approximately 1% of HIV-
8 positive patients without AIDS and 18% of those with AIDS [43], based on a prevalence of
9 71,300 HIV-positive patients in 2013 in Canada including 218 with AIDS [10].

10
11 EC is an AIDS-defining illness affecting nearly 20% of patients AIDS [44], thus at least 43
12 cases of EC are expected to occur annually in Canada. EC is also associated with other
13 underlying conditions (eg. receipt of corticosteroids), but data on infection rates in these
14 populations are not sufficient to inform accurate estimates.

15
16 Our study found that approximately 3,000 invasive fungal infections occur annually in
17 Canada, while over half a million people suffer from a chronic *Candida* or *Aspergillus*
18 infection. Overall, RVVC is likely the most frequent serious fungal disease in Canada, with
19 substantial quality of life impairment [45] and health costs [46], prompting the need for
20 specific guidelines addressing diagnostic and treatment. Education on current guidelines for
21 non-invasive forms of pulmonary aspergillosis is needed to increase awareness, diagnosis and
22 treatment proficiency among health care providers. Invasive fungal infections annual
23 incidence (8.3/100,000) is similar to that of invasive pneumococcal disease (8.9 in 2014) and
24 higher than invasive *S. pyogenes* disease (4.7 in 2013), infectious syphilis (5.1 in 2011),
25 tuberculosis (4.4 in 2014) and HIV (5.9 in 2013) all regarded as important in Canada [47].

1 Amongst invasive infections, candidiasis is by far the most common disease, followed by
2 aspergillosis. Cryptococcosis, pneumocystosis and endemic mycoses are less commonly
3 encountered, consistent with findings of a recent large registry across North America [48].
4 Invasive fungal infections data from two Canadian centers have confirmed 90-day fatality
5 rates of 41% and 36% for IC and IA, respectively [49], over a thousand deaths annually in
6 Canada.

7
8 Our estimates of serious fungal infection burden in Canada provide an opportunity for both
9 health care providers and public health agencies to improve diagnostics, surveillance and
10 formal epidemiological studies, including measures of health care utilization.

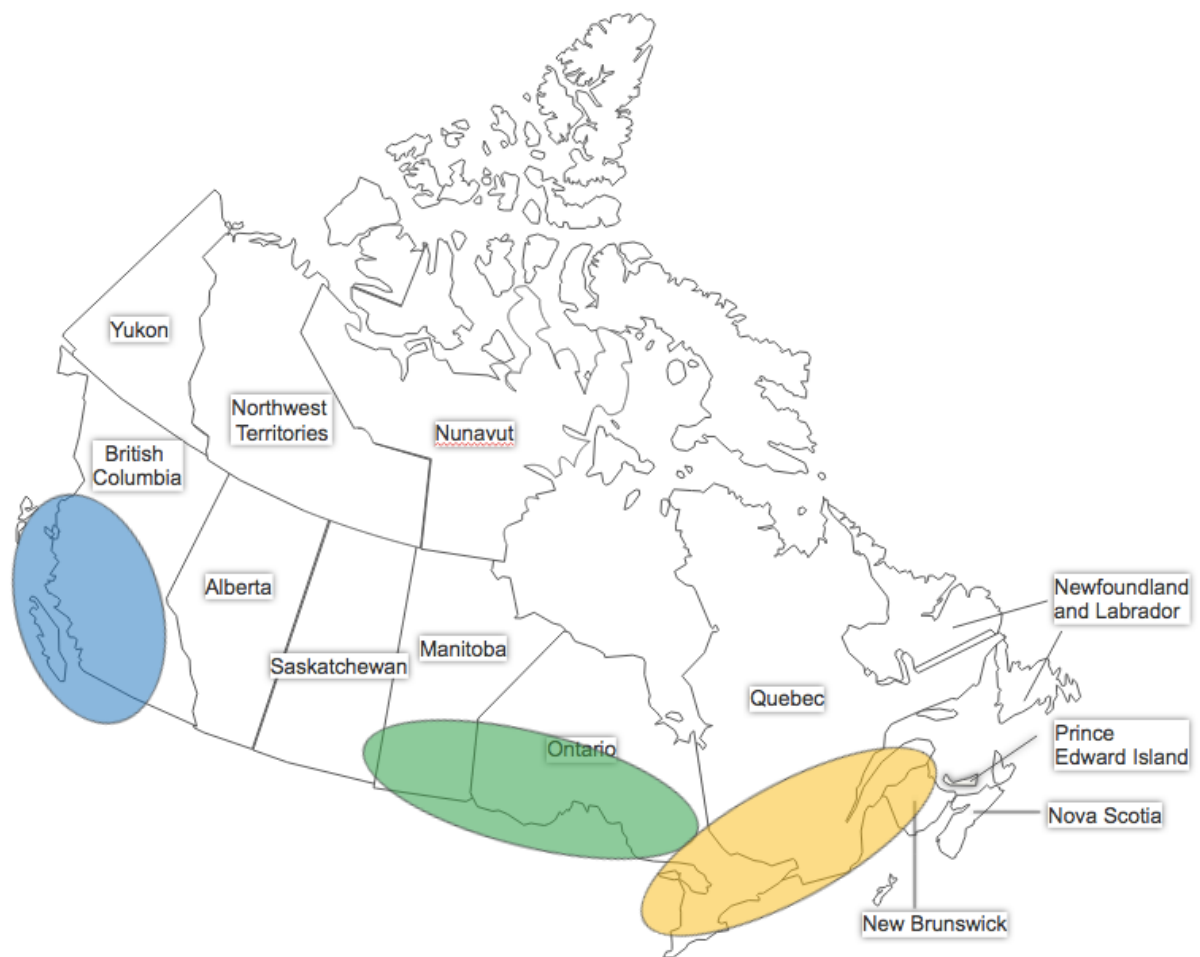
1 Tables & Figures

2 Table 1. Estimated annual burden of serious fungal diseases in Canada.

Serious fungal infection categories and types	Proportion affected (per 100,000 population)	# cases
Opportunistic invasive fungal infections	8,28	2,949
Invasive candidiasis (IC) without candidemia	2,91	1,034
Candidemia	2,91	1,034
Invasive aspergillosis (IA)	1,59	566
<i>Pneumocystis pneumonia</i> (PCP)	0,69	252
Cryptococcosis	0,18	63
Endemic mycoses	0,28	99
Blastomycosis	0,18	63
Histoplasmosis	0,08	27
Coccidioidomycosis	0,03	9
Non-invasive pulmonary aspergillosis	381,79	135,690
Severe asthma with fungal sensitization (SAFS)	206,37	73,344
Allergic bronchopulmonary aspergillosis (ABPA)	174,04	61,854
Chronic pulmonary aspergillosis (CPA)	1,38	492
Mucosal candidiasis	1,446,94	514,250
Recurrent vulvovaginal candidiasis (RVVC)	1,403,16	498,688
Oropharyngeal candidiasis (OC)	43,67	15,519
Esophageal candidiasis (EC)	0,12	43

3
4

Figure 1. Localization of geographically-confined mycoses in Canada. Colored areas represent the approximate geographic distribution of three fungal infections: Blue: *C. gattii*; Green: blastomycosis; Yellow: blastomycosis and histoplasmosis.



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