Eur J Clin Microbiol Infect Dis (2017) 36:987–992
DOI 10.1007/s10096-017-2922-y

ORIGINAL ARTICLE

Serious fungal infections in Canada

S. F. Dufresne[1] · D. C. Cole[2] · D. W. Denning[3] · D. C. Sheppard[4]

Received: 21 December 2016 / Accepted: 21 December 2016 / Published online: 4 February 2017

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 modeling, as per a methodology previously described by the LIFE program (http://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 bronchopulmonary aspergillosis are the most frequent infections, with population prevalences of 498,688 (1403/100,000), 73,344 (206/100,000), and 61,854 (174/100,000) cases, respectively. Over 3000 invasive fungal infections are estimated to occur annually, with incidences of 2068 cases (5.8/100,000) of invasive candidiasis, 566 cases (1.6/100,000) of invasive aspergillosis, 252 cases (0.71/100,000) 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.

✉ S. F. Dufresne
sf.dufresne@umontreal.ca

[1] Department of Infectious Diseases and Medical Microbiology, Maisonneuve-Rosemont Hospital Research Center, Université de Montréal, Montréal, Canada

[2] Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

[3] The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

[4] Department of Microbiology and Immunology and Department of Medicine, Infectious Diseases and Immunity in Global Health Program, Research Institute of the McGill University Health Center, McGill University, Montréal, Canada

Introduction

Canada is a high-income country with a gross domestic product of 1551 billion dollars (USD) in 2015 (GDP per capita, 43,249). Several studies have examined the epidemiology of fungal infections in Canada, but most were local (single-centered, regional, or provincial) and focused on individual infections in specific populations. A single study reported on the burden of invasive fungal infections at the national level; however, these data are over 20 years old [1] and relied largely on clinical microbiology laboratory records review. Since that time, the Canadian population has expanded by 26%; use of immunosuppressive therapies that increase the risk of fungal infection have risen in importance, e.g., solid organ and stem cell transplantation and immunosuppressive biologic therapies; fungal diagnostics have improved; and medical care practices have evolved greatly. Hence, we sought to provide an estimate of the national burden of serious fungal infections.

Materials and methods

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

In brief, an annual burden was estimated for each targeted serious fungal disease and presented as: (i) absolute number of cases per year in Canada (representing either incident or prevalent cases, depending on the nature of the infection) and (ii) annual rates (incidence or prevalence), using the annual number of cases as the numerator and the entire Canadian 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 gray 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 Blood and Marrow Transplant Group (number of hematopoietic stem cell transplants), the Organisation for Economic Co-operation and Development (number of chronic obstructive pulmonary disease [COPD] admissions) [9], the Public Health Agency of Canada (human immunodeficiency virus [HIV] prevalence and acquired immune deficiency syndrome [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 estimated at pro rata of the 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 Fig. 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-years over a 5-year period, based on blood and cerebrospinal fluid culture (approximately 93% of cases were candidemia). Of note, the 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 1034 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 2068 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 (SOT) recipients, as well as patients with severe COPD. A recent study from a Montreal center found an incidence of 8.9% among adult acute leukemia patients (both myelogenous [AML] and lymphocytic [ALL]) [16], consistent with other international reports [17]. There were 1215 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

Table 1 Estimated annual burden of serious fungal diseases in Canada

Serious fungal infection categories and types	Proportion affected (per 100,000 population)	No. of cases
Opportunistic invasive fungal infections	**8.28**	**2949**
Invasive candidiasis (IC) without candidemia	2.91	1034
Candidemia	2.91	1034
Invasive aspergillosis (IA)	1.59	566
Pneumocystis pneumonia (PCP)	0.71	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	**1446.94**	**514,250**
Recurrent vulvovaginal candidiasis (RVVC)	1403.16	498,688
Oropharyngeal candidiasis (OC)	43.67	15,519
Esophageal candidiasis (EC)	0.12	43

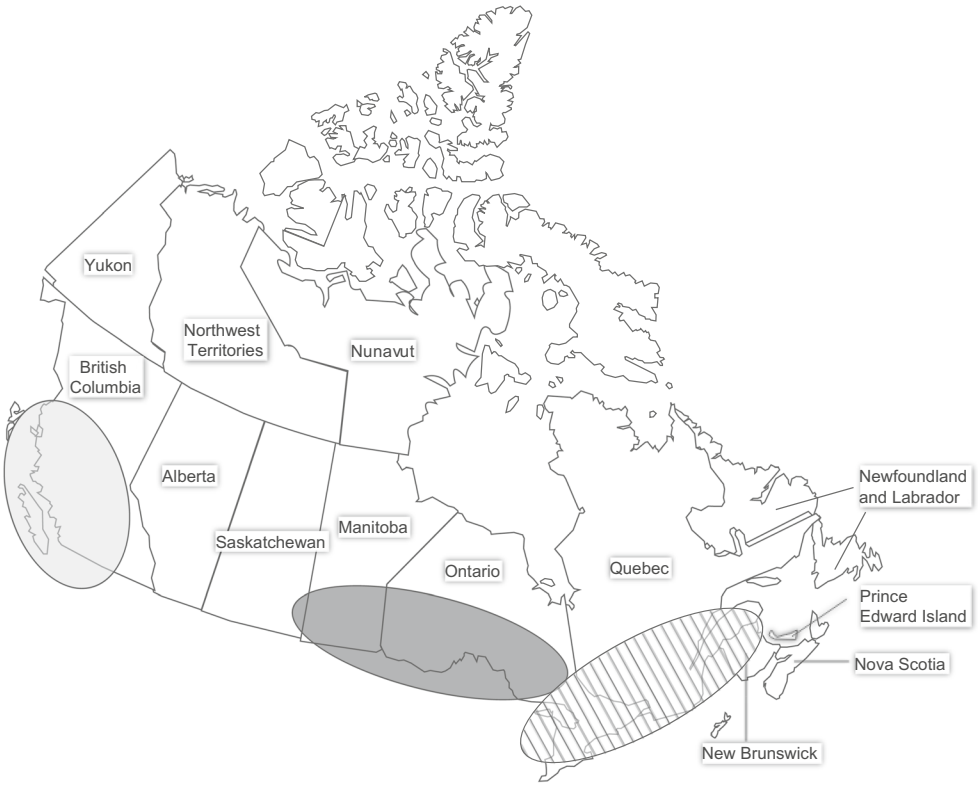

Fig. 1 Localization of geographically confined mycoses in Canada. The colored areas represent the approximate geographic distribution of three fungal infections: *light gray* *Cryptococcus gattii*; *dark gray* blastomycosis; *hatched* blastomycosis and histoplasmosis

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 1358, 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 1200 allogeneic HSCTs are performed annually in Canada (personal communication, Canadian Blood and Marrow Transplant Group), resulting in an additional estimated 90 cases of IA per year. Of note, large prospective cohort studies found that at least 20% of IA cases occur more than a year after SOT and HSCT [19, 24], 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 COPD [9] account for approximately 214 IA cases, or 3.6 cases per 1000 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 center 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 Québec'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] (Fig. 1). Between 2010 and 2013, a mean of 23 *C. gattii* infections per year were reported to the British Columbia Centre for Disease Control [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 (Fig. 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 and, hence, in Canada.

Histoplasmosis occurs mainly along the Saint Lawrence river valley, in Ontario and Québec (Fig. 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 that there are between 2 and 9 cases of coccidioidomycosis annually, largely in returning travelers [1, 35].

Non-invasive pulmonary aspergillosis

Extrapolating from pulmonary tuberculosis 2014 annual incidence data ($n = 1065$) [11], the prevalence of CPA following tuberculosis was 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; $n = 4077$) [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

Recurrent vulvovaginal candidiasis (RVVC) is reported to affect up to 9% of women of reproductive age [41]. The 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.

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

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

Our study found that approximately 3000 invasive fungal infections occur annually in Canada, while over half a million people suffer from a chronic *Candida* or *Aspergillus* infection. Overall, RVVC is likely the most frequent serious fungal disease in Canada, with substantial quality of life impairment [45] and health costs [46], prompting the need for specific guidelines addressing diagnostics and treatment. Education on current guidelines for non-invasive forms of pulmonary aspergillosis is needed to increase awareness, diagnosis, and treatment proficiency among healthcare providers. Invasive fungal infections annual incidence (8.3/100,000) is similar to that of invasive pneumococcal disease (8.9 in 2014) and higher than invasive *Streptococcus pyogenes* disease (4.7 in 2013), infectious syphilis (5.1 in 2011), tuberculosis (4.4 in 2014), and HIV (5.9 in 2013), all regarded as important infectious diseases in Canada [47]. Amongst invasive infections, candidiasis is by far the most common disease, followed by aspergillosis. Cryptococcosis, pneumocystosis, and endemic mycoses are less commonly encountered, consistent with findings of a recent large registry across North America [48]. Invasive fungal infections data from two Canadian centers have confirmed 90-day fatality rates of 41% and 36% for IC and IA, respectively [49], representing over a thousand deaths annually in Canada.

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

References

1. Nicolle L, Rotstein C, Bourgault A, St-Germain G, Garber G; Canadian Infectious Diseases Society Invasive Fungal Registry (1998) Invasive fungal infections in Canada from 1992 to 1994. Can J Infect Dis 9(6):347–352
2. Rodriguez-Tudela JL, Alastruey-Izquierdo A, Gago S, Cuenca-Estrella M, León C, Miro JM, Nuñez Boluda A, Ruiz Camps I, Sole A, Denning DW; University of Manchester in association with the LIFE program (2015) Burden of serious fungal infections in Spain. Clin Microbiol Infect 21(2):183–189. doi:10.1016/j.cmi.2014.07.013
3. Ruhnke M, Groll AH, Mayser P, Ullmann AJ, Mendling W, Hof H, Denning DW; University of Manchester in association with the

LIFE program (2015) Estimated burden of fungal infections in Germany. Mycoses 58(Suppl 5):22–28. doi:10.1111/myc.12392
4. Statistics Canada. Table 051-0001. Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted). CANSIM (database)
5. Statistics Canada. Table 105-0502. Health indicator profile, two year period estimates, by age group and sex, Canada, provinces, territories, health regions (2013 boundaries) and peer groups, occasional. CANSIM (database)
6. Canadian Cancer Society (2015) Acute myelogenous leukemia statistics. Available online at: http://www.cancer.ca/en/cancer-information/cancer-type/leukemia-acute-myelogenous-aml/statistics/?region=on. Accessed 10 Apr 2015
7. Canadian Cancer Society's AdvisoryCommittee on Cancer Statistics (2015) Canadian Cancer Statistics. Canadian Cancer Society, Toronto, Ontario
8. Canadian Institute for Health Information (CIHI) (2014) Canadian organ replacement register annual report: treatment of end-stage organ failure in Canada, 2003 to 2012. CIHI, Ottawa, Ontario
9. Organisation for Economic Co-operation and Development (OECD) (2013) Health at a glance 2013: OECD indicators (2013). OECD Publishing
10. Public Health Agency of Canada (2014) HIV and AIDS in Canada: surveillance report to December 31, 2013. Minister of Public Works and Government Services Canada, Ottawa, Ontario
11. World Health Organization (WHO) (2014) Tuberculosis country profiles: Canada. Available online at: https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=CA&LAN=EN&outtype=html. Accessed 16 Aug 2016
12. Cystic Fibrosis Canada (2015) The Canadian Cystic Fibrosis Registry: 2013 annual report
13. Laupland KB, Gregson DB, Church DL, Ross T, Elsayed S (2005) Invasive Candida species infections: a 5 year population-based assessment. J Antimicrob Chemother 56(3):532–537. doi:10.1093/jac/dki258
14. St-Germain G, Laverdière M, Pelletier R, René P, Bourgault AM, Lemieux C, Libman M (2008) Epidemiology and antifungal susceptibility of bloodstream Candida isolates in Quebec: Report on 453 cases between 2003 and 2005. Can J Infect Dis Med Microbiol 19(1):55–62
15. Clancy CJ, Nguyen MH (2013) Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis 56(9):1284–1292. doi:10.1093/cid/cit006
16. Barkati S, Dufresne SF, Bélanger S, Vadnais B, Bergeron J, Labbé AC, Laverdière M (2014) Incidence of invasive aspergillosis following remission-induction chemotherapy for acute leukemia: a retrospective cohort study in a single Canadian tertiary care centre. CMAJ Open 2(2):E86–E93. doi:10.9778/cmajo.20130062
17. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, Pastore D, Picardi M, Bonini A, Chierichini A, Fanci R, Caramatti C, Invernizzi R, Mattei D, Mitra ME, Melillo L, Aversa F, Van Lint MT, Falcucci P, Valentini CG, Girmenia C, Nosari A (2006) The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. Haematologica 91(8):1068–1075
18. Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, Apewokin S, Horn DL (2012) Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infect 65(5):453–464. doi:10.1016/j.jinf.2012.08.003
19. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM (2010) Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 50(8):1101–1111. doi:10.1086/651262
20. Corzo-León DE, Satlin MJ, Soave R, Shore TB, Schuetz AN, Jacobs SE, Walsh TJ (2015) Epidemiology and outcomes of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens. Mycoses 58(6):325–336. doi:10.1111/myc.12318
21. Harrison N, Mitterbauer M, Tobudic S, Kalhs P, Rabitsch W, Greinix H, Burgmann H, Willinger B, Presterl E, Forstner C (2015) Incidence and characteristics of invasive fungal diseases in allogeneic hematopoietic stem cell transplant recipients: a retrospective cohort study. BMC Infect Dis 15:584. doi:10.1186/s12879-015-1329-6
22. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, Gersten ID, Mendizabal AM, Leather HL, Confer DL, Maziarz RT, Stadtmauer EA, Bolaños-Meade J, Brown J, Dipersio JF, Boeckh M, Marr KA; Blood and Marrow Transplant Clinical Trials Network (2010) Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood 116(24):5111–5118. doi:10.1182/blood-2010-02-268151
23. Montesinos P, Rodríguez-Veiga R, Boluda B, Martínez-Cuadrón D, Cano I, Lancharro A, Sanz J, Arilla MJ, López-Chuliá F, Navarro I, Lorenzo I, Salavert M, Pemán J, Calvillo P, Martínez J, Carpio N, Jarque I, Sanz GF, Sanz MA (2015) Incidence and risk factors of post-engraftment invasive fungal disease in adult allogeneic hematopoietic stem cell transplant recipients receiving oral azoles prophylaxis. Bone Marrow Transplant 50(11):1465–1472. doi:10.1038/bmt.2015.181
24. Kontoyiannis DP, Marr KA, Park BJ, Alexander BD, Anaissie EJ, Walsh TJ, Ito J, Andes DR, Baddley JW, Brown JM, Brumble LM, Freifeld AG, Hadley S, Herwaldt LA, Kauffman CA, Knapp K, Lyon GM, Morrison VA, Papanicolaou G, Patterson TF, Perl TM, Schuster MG, Walker R, Wannemuehler KA, Wingard JR, Chiller TM, Pappas PG (2010) Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 50(8):1091–1100. doi:10.1086/651263
25. Guinea J, Torres-Narbona M, Gijón P, Muñoz P, Pozo F, Peláez T, de Miguel J, Bouza E (2010) Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. Clin Microbiol Infect 16(7):870–877. doi:10.1111/j.1469-0691.2009.03015.x
26. Kidd SE, Hagen F, Tscharke RL, Huynh M, Bartlett KH, Fyfe M, Macdougall L, Boekhout T, Kwon-Chung KJ, Meyer W (2004) A rare genotype of Cryptococcus gattii caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada). Proc Natl Acad Sci U S A 101(49):17258–17263. doi:10.1073/pnas.0402981101
27. BC Centre for Disease Control (2014) British Columbia Annual Summary of Reportable Diseases 2013. Communicable Disease Prevention and Control Services (CDPACS), Provincial Health Services Authority Vancouver, British Columbia
28. Dalcin D, Ahmed SZ (2015) Blastomycosis in northwestern Ontario, 2004 to 2014. Can J Infect Dis Med Microbiol 26(5):259–262
29. Morris SK, Brophy J, Richardson SE, Summerbell R, Parkin PC, Jamieson F, Limerick B, Wiebe L, Ford-Jones EL (2006) Blastomycosis in Ontario, 1994–2003. Emerg Infect Dis 12(2):274–279. doi:10.3201/eid1202.050849
30. Litvinov IV, St-Germain G, Pelletier R, Paradis M, Sheppard DC (2013) Endemic human blastomycosis in Quebec, Canada, 1988–

2011. Epidemiol Infect 141(6):1143–1147. doi:10.1017/s0950268812001860
31. Government of Manitoba (2014) Manitoba Annual Summary of Communicable Diseases 2013. Epidemiology & Surveillance, Public Health Branch, Public Health and Primary Health Care Division, Manitoba Health, Healthy Living and Seniors
32. Guy R, Roy O, Poupart G, Panisset M (1949) Histoplasmin sensitivity; preliminary observations in a group of school children in the Province of Quebec. Can J Public Health 40(2):68–71
33. Leznoff A, Frank H, Taussig A, Brandt JL (1969) The focal distribution of histoplasmosis in Montreal. Can J Public Health 60(8): 321–325
34. MacEachern EJ, McDonald JC (1971) Histoplasmin sensitivity in McGill University students. Can J Public Health 62(5):415–422
35. Sekhon AS, Isaac-Renton J, Dixon JM, Stein L, Sims HV (1991) Review of human and animal cases of coccidioidomycosis diagnosed in Canada. Mycopathologia 113(1):1–10
36. Denning DW, Pleuvry A, Cole DC (2011) Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. Bull World Health Organ 89(12):864–872. doi:10.2471/blt.11.089441
37. Smith NL, Denning DW (2011) Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. Eur Respir J 37(4):865–872. doi:10.1183/09031936.00054810
38. Denning DW, Pleuvry A, Cole DC (2013) Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. Med Mycol 51(4):361–370. doi:10.3109/13693786.2012.738312
39. Baxter CG, Dunn G, Jones AM, Webb K, Gore R, Richardson MD, Denning DW (2013) Novel immunologic classification of aspergillosis in adult cystic fibrosis. J Allergy Clin Immunol 132(3):560–566.e10. doi:10.1016/j.jaci.2013.04.007
40. Agarwal R (2011) Severe asthma with fungal sensitization. Curr Allergy Asthma Rep 11(5):403–413. doi:10.1007/s11882-011-0217-4
41. Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J (2013) Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. J Low Genit Tract Dis 17(3):340–345. doi:10.1097/LGT.0b013e318273e8cf
42. Lalla RV, Latortue MC, Hong CH, Ariyawardana A, D'Amato-Palumbo S, Fischer DJ, Martof A, Nicolatou-Galitis O, Patton LL, Elting LS, Spijkervet FK, Brennan MT; Fungal Infections Section, Oral Care Study Group, Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) (2010) A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer 18(8):985–992. doi:10.1007/s00520-010-0892-z
43. Matee MI, Scheutz F, Moshy J (2000) Occurrence of oral lesions in relation to clinical and immunological status among HIV-infected adult Tanzanians. Oral Dis 6(2):106–111
44. Buchacz K, Baker RK, Palella FJ Jr, Chmiel JS, Lichtenstein KA, Novak RM, Wood KC, Brooks JT; HOPS Investigators (2010) AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. AIDS 24(10):1549–1559. doi:10.1097/QAD.0b013e32833a3967
45. Zhu YX, Li T, Fan SR, Liu XP, Liang YH, Liu P (2016) Health-related quality of life as measured with the Short-Form 36 (SF-36) questionnaire in patients with recurrent vulvovaginal candidiasis. Health Qual Life Outcomes 14:65. doi:10.1186/s12955-016-0470-2
46. Fong IW (1996) Clinical and cost considerations in the pharmacotherapy of vulvovaginal candidiasis. Pharmacoeconomics 9(6): 497–505
47. Public Health Agency of Canada (2016) Surveillance. Available online at: http://www.phac-aspc.gc.ca/surveillance-eng.php. Accessed 16 Sep 2016
48. Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, Horn D (2012) The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. Diagn Microbiol Infect Dis 73(4):293–300. doi:10.1016/j.diagmicrobio.2012.06.012
49. Haider S, Rotstein C, Horn D, Laverdiere M, Azie N (2014) The Prospective Antifungal Therapy Alliance(®) registry: A two-centre Canadian experience. Can J Infect Dis Med Microbiol 25(1):17–23